JPRS-ULS-91-018
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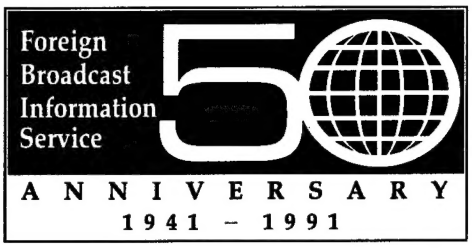
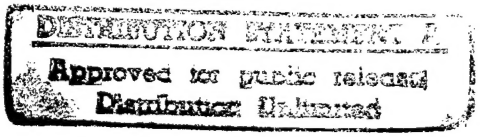


JPRS Report

Science & Technology

USSR: Life Sciences



Science & Technology
USSR: Life Sciences

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917C0274A Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 16 No 8, Aug 90 (manuscript received 13 Feb 90) pp 1013-1018

[Article by G. I. Kovalevskaya, V. N. Pashkov, O. V. Bulgakov, I. M. Fedorova*, L. G. Magazanik* and Ye. V. Grishin**, Branch of Institute of Bioorganic Chemistry imeni M. M. Shemyakin, USSR Academy of Sciences, Pushchino, Moskovskaya Oblast; *Institute of Evolutionary Physiology and Biochemistry imeni I. M. Sechenov, USSR Academy of Sciences, Leningrad, and **Institute of Bioorganic Chemistry imeni M. M. Shemyakin, USSR Academy of Sciences, Moscow]

UDC 577.112.088.3:615.919:595.44-114.52.088

[Abstract] A protein insect toxin (α-latroinsectotoxin, LIT) was isolated and identified from the venom of *Latrodectus mactans tredecimguttatus* spider by chromatography on an ion-exchange resin Mono Q at pH 8.0 in NaCl concentration gradient. Molecular weight of LIT was determined to be in the range of 120 kDa; glutaminic acid was identified as the N-terminal amino acid residue. LIT consists of several polypeptides with isoelectric points clustering around 5.2-5.4. A 20 ng/individual dose of LIT paralyzed 100 percent of the fly larvae used. LIT concentrations of 4.2×10^{-10} M increased the frequency of intracellular miniature excitatory potentials in blowfly larvae muscle fibers; a dose of 1.2×10^{-7} M of LIT showed no effect on the neuromuscular junction of the frog. Figures 3; references 15: 5 Russian, 10 Western.

Construction of a Complete Library of Mutants at Region -35 of Model Prokaryotic Promoter

917C0274B Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 16 No 8, Aug 90 (manuscript received 23 Oct 89) pp 1052-1059

[Article by V. L. Drutsa, A. V. Krivonos, O. N. Koroleva and Z. A. Shabarova, Department of Chemistry and Interdepartmental Problematic Scientific Research, Laboratory of Molecular Biology and Bioorganic Chemistry imeni A. N. Belozerskiy, Moscow State University imeni M. V. Lomonosov]

UDC 577.113.6+577.212.2

[Abstract] The researchers proposed an economic synthetic approach to investigations of nucleotide variability in conservative regions (2-8 bp) of functionally important DNA fragments. It is based on simultaneous synthesis of a complete set of DNA fragments including all or virtually all variations of nucleotide replacements in the fragment under investigation, which ideally should have identical or uniform fractional composition. This translates to preparation and analysis of 10^2-10^4 mutants from which the compositions of various functional structures and specific nucleotide replacements were to be determined having little or no effect on the consensus function. In the present paper, problems of chemical synthesis of mixed oligonucleotides were analyzed. The chemical-enzymatic synthesis of a complete library of 40-bp DNA duplexes corresponding to the model prokaryotic promoter and differing in 6-member segments at the -35 region was described. Synthetic characteristics were identified along with isolation and sequencing of oligodesoxyribonucleotides containing extended variable fragments. Figures 3; references 24: 7 Russian, 17 Western.

Characteristics of an Oligosaccharide Isolated From *Micrococcus Lysodeikticus (Luteus)* Bacterium and Converted Into a Long-Lived Radical State as the Result of the Loss of an Electron

917C0274C Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 16 No 8, Aug 90 (manuscript received 10 Apr 89, after final revision 10 Oct 89) pp 1073-1079

[Article by V. I. Binyukov, S. I. Stepanov, G. D. Tantsyrev*, Ye. F. Kharatyan, A. S. Shashkov** and D. N. Ostrovskiy, Institute of Biochemistry imeni A. N. Bakh, USSR Academy of Sciences, Moscow; *Institute of Energetic Problems of Chemical Physics, USSR Academy of Sciences, Moscow; **Institute of Organic Chemistry imeni N. D. Zelinskiy, USSR Academy of Sciences, Moscow]

UDC 577.352.38:579.222'114

[Abstract] An earlier study performed by the authors isolated a compound from the cells of *Micrococcus Lysodeikticus* bacteria that, in the presence of a weak oxidizer, converted to a long-lived free radical. In the present work it was shown that this compound is a nitrogen-containing trisaccharide in which the nitrogen is a part of the paramagnetic center. Based on the data obtained from the NMR and ESR spectra and from isotope substitution, it was concluded that this compound is 6-O-(2-desoxy-2-(N-methyl)hydroxyamino-β-D-glucopyranosyl)-α,α-trehalose, called lysodectose. The paramagnetic center was localized at the nitrosyl group of the oxidized moiety of the molecule. This compound's participation in biological reactions is not clear as yet, but, based on other compounds with paramagnetic centers, an assumption was made that it will play an important role in the metabolism of bacteria cells. Figures 1; references 20: 10 Russian, 10 Western.

Characteristics of Glutamic Acid Derivatives Isolated From Brevibacteria and Converted to Long-Lived Radical State by a Loss of an Electron

917C0274D Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 16 No 8, Aug 90 (manuscript received 19 Apr 89, after final revision 5 Jul 89) pp 1080-1088

[Article by V. I. Binyukov, N. M. Bazdyreva, G. D. Tantsyrev*, Ye. F. Kharatyan, A. S. Shashkov**, K. B. Shumayev and D. N. Ostrovskiy, Institute of Biochemistry imeni A. N. Bakh, USSR Academy of Sciences, Moscow; *Institute of Energetic Problems in Chemical Physics, USSR Academy of Sciences, Moscow; and **Institute of Organic Chemistry imeni N. D. Zelinskiy, USSR Academy of Sciences, Moscow]

UDC 579.222.7'12.389+577.352.38

[Abstract] A compound containing a paramagnetic center was isolated from *Brevibacterium ammoniagenes* and characterized in detail. It was given the name ammonigenin. Based on the data from IR, NMR and EPR spectroscopy, it was identified as a derivative of glutamic acid: lactone of N-hydroxy-N-(2-carbamoylethyl)glutamyl-4-amino-2-hydroxybutylamide. Its paramagnetic center was localized at the nitrosyl-group-containing terminal of the molecule. It was speculated that this compound participates in protection of bacterial cells from external factors. Figures 5; references 16: 8 Russian, 8 Western.

Isolation and Properties of Insect-Specific Neurotoxins From Venom of *Latrodectus mactans tredecimguttatus* Spider

917C0274E Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 16 No 8, Aug 90 (manuscript received 16 Mar 90) pp 1138-1140

[Article by V. G. Krasnoperov, O. G. Shamotiyenko and Ye. G. Grishin*, Branch of Institute of Bioorganic Chemistry imeni M. M. Shemyakin, USSR Academy of Sciences, Pushchino, Moskovskaya Oblast; *Institute of Bioorganic Chemistry imeni M. M. Shemyakin, USSR Academy of Sciences, Moscow]

UDC 577.112.088.3:591.145.2-544

[Abstract] The venom of the *Latrodectus mactans tredecimguttatus* spider contains α-latrotoxin and a series of toxic protein components stimulating presynaptic activity of invertebrates' nerve cells. A method was developed for separation of five of these individual toxins by means of chromatography on hydroxyapatite column and an ion exchange chromatography on Mono Q and Mono S columns. The LD_{50} values of these toxins were determined on the large wax moth *Galleria metonella.* All toxins showed lethal effect towards cockroaches *Periplaneta americana.* On BALBc mice no toxic effect was observed at doses exceeding 5 mg/kg body weight. All of them could be stored for up to two weeks at 4°C without losing their activity. Figures 1; references 5: 1 Russian, 4 Western.

Direct Measurement of Light-Induced Na^+-Dependent Transmembrane Potential in Cyanobacteria Lingbia Confervoides

917C0307A Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 12, Dec 90 (manuscript received 17 May 90) pp 1271-1274

[Article by I. I. Broun, V. D. Taranenko, I. V. Timofeyev and Ye. S. Timofeyeva, Laboratory of Biological Problems, Chair of Human and Animal Physiology, Odessa State University imeni I. I. Mechnikov]

UDC 577.23:579.843.1

[Abstract] Direct microelectrode measurements demonstrated that continuous illumination from a 75 W halogen lamp resulted in a 2-6 mV increase in the transmembrane potentials of cyanobacteria Lingbia confervoides. After illumination the transmembrane potential of the cytoplasmic membrane decreased to baseline. Application of protonophore ClCCP abolished the light-induced change in the the transmembrane potential, while addition of NaCl led to recovery of the response to light. Sodium sulfate was somewhat less effective than NaCl. Finally, application of Na^+/H^+ antiporter monensin did not interfere with light-induced changes in the transmembrane potential, but prevented the response to light in systems already exposed to NaCl and ClCCP. The data demonstrated that translocation of Na^+ is involved in the generation of light-induced transmembrane potential in the presence of a protonophore. Accordingly, this study represents the first demonstration of light-induced electrogenesis coupled to sodium energetics rather than the proton pump in the halophilic bacterium. Figures 3; references 8: 2 Russian, 6 Western.

Oubain Effects on Acetylcholine-Activated Cl Ion Channels in Neural Membranes of Helix Pomatia

917C0307B Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 12, Dec 90 (manuscript received 11 Aug 90) pp 1302-1309

[Article by V. L. Arvanov, P. D. Brezhestovskiy* and S. N. Ayrapetyan, Institute of Experimental Biology, Armenian SSR Academy of Sciences, Yerevan; *Institute of Experimental Cardiology, All-Union Cardiological REsearch Center, USSR Academy of Medical Sciences, Moscow]

UDC 591.18:577.35:594.38:615.787

[Abstract] Neurons isolated from the ganglia of the edible snail Helix pomatia were used to assess the mechanism of action of oubain on acetylcholine-activated Cl ion channels. The results of electrophysiological studies on neurons and membrane fragments demonstrated that oubain-mediated loss of membrane sensitivity to acetylcholine was not due to direct interference with acetylcholine effects on the ion channels. Rather, the data on the temporal parameters of oubain-induced desensitization were consistent with inactivation of the sodium pump and disruption in second messenger mechanisms. Figures 6; tables 1; references 15: 7 Russian, 8 Western.

Electrical Properties of Surfaces of Stearic Acid Langmuir Films

917C0307C Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 12, Dec 90 (manuscript received 23 Apr 90) pp 1323-1327

[Article by N. G. Sukhodolov, L. G. Levashova, S. Yu. Pavlov and A. I. Yanklovich, Leningrad State University]

UDC 539.233+541.183.02

[Abstract] An analysis was conducted on electric characteristics of surfaces of regular Langmuir-Blodgett films prepared from stearate salts vis-a-vis pH and $BaCl_2$ or $CdCl_2$ concentration, as well as on dispersions obtained after ultrasonication of the monolayers. Analysis of electrophoretic mobilities and streaming potentials revealed parallel patterns for ζ-pH and ζ-log c plots, where c = concentration of electrolyte, for the regular films and dispersions. Consequently, it appears that surfaces of such dispersions are quite similar to those of regular Langmuir-Blodgett films, indicating that they are not unordered, almost amorphous, structural system. In addition, the fact that the ζ-log c plots were almost linear suggests that such systems may have potential use as chemical sensors. Figures 2; references 8: 6 Russian, 2 Western.

Structural Effects of Electromagentic Waves on Molecular Layers

917C0307D Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 12, Dec 90 (manuscript received 23 Jun 90) pp 1328-1232

[Article by Yu. B. Gaydidey and A. S. Trofimov, Institute of Theoretical Physics, Ukrainian SSR Academy of Sciences, Kiev]

UDC 541.143:536.758

[Abstract] Based on observations that polarized electromagnetic radiation induced anisotropy in Langmuir films prepared from azo dyes, a theoretical analysis was conducted to extrapolate such data to biological membranes and bilayer lipid membranes. Employing the mathematics of statistical mechanics resulted in the demonstration that, on theoretical grounds, polarizing electromagnetic radiation may be expected to alter the potential energy minimum of the various domains, while not altering their location. Accordingly, initially equivalent domains lose energetic equivalence while temperature-related molecular fluctuations lead to molecular reorientation. The original molecular arrangement is recovered after exposure as a result of relaxation processes. Figures 2; references 4: 2 Russian, 2 Western.

Proceedings of the Sessions of the Leningrad Scientific Society of Therapists imeni S. P. Botkin

917C0216 Moscow TERAPEVTICHESKIY ARKHIV in Russian Vol 62 No 12, Dec 90 pp 133-137

[Selected abstract of report by A. G. Rakhmanova, V. K. Prigozhina, G. V. Volkova, G. V. Bogoyavlenskiy, N. P. Glukhov, G. A. Makarenko, A. Yu. Kolmakov, V. A. Isakov, Yu. A. Fomin, and M. D. Chernykh, presented on 16 January 1990, with Professor G. B. Fedoseyev presiding as chairman, and Candidate of Medical Sciences I. N. Orlova as secretary; report appears under the rubric "Reports" and is titled "HIV-Positive Tests and AIDS, From Materials From the Center for AIDS in Leningrad (Clinical-Laboratory and Clinical-Epidemiological Data); report is followed by the closing remarks of Professor Fedoseyev]

[Excerpt] [Passage omitted] An analysis of the work of the Leningrad Center for for the Prevention and Control of AIDS showed that 45 seropositive individuals were detected during the testing of more than 1 million residents for HIV-infection: 24 were our countrymen (19 Leningrad residents, two visitors from other cities, and three anonymous examinees with undetermined place of residence), and 21 were foreign citizens. The clinical-laboratory data made it possible to diagnose AIDS in four of the seropositive individuals, one of whom (a female) has already died. In the remaining HIV-infected individuals, virus-carrier stages of persistent generalized lymphadenopathy and of AIDS-related complex were established. We should turn our atention to the groups of people who have undergone a comprehensive clinical-laboratory and epidemiological examination—80 individuals who came into contact with HIV-infected individuals, and some 900 with dubious results of enzyme immunoassay and immune blotting.

[Closing remarks of the chairman] In his closing remarks, the chairman, Professor G. B. Fedoseyev, [pointed out] that a rapid growth in the AIDS morbidity rate and in the carriage of HIV-infection is being forecast as we approach the year 2000. Medications for the treatment of AIDS have appeared. However the number of patients treated with them is small, and it is still not possible to cure the disease. Laboratory techniques represent a rather reliable method for diagnosing the disease. The personal initiative and the efforts of Professor A. G. Rakhmanova and her department have produced positive results. At the present time, 2 million rubles have been allocated for combating AIDS. It is disturbing that this auditorium today is only 20 percent filled and that many practicing physicians have not received information they need on this disease.

Environmental Pollution in Soviet Georgia

917C0398C Tbilisi SOOBSHCHENIYA AKADEMII NAUK GRUZINSKOY SSR in Russian Vol 140 No 1, Jan 91 (manuscript received 7 Sep 90) pp 77-80

[Article by K. A. Tavartkiladze and E. V. Sadzhaya, Geography Institute imeni Vakhusti Bagrationi, Georgian SSR Academy of Sciences]

UDC 551.510.42

[Abstract] The changes in atmospheric pollution in five cities in Soviet Georgia (Sukhumi, Senaki, Telavi, Anaseuli, and Tsalka) as measured by the aerosol optical density from 1969 through 1985 were investigated to determine their effect on the formation of physical atmospheric parameters. The results demonstrated that the region is gradually becoming more polluted, with the peak in pollution noted in 1983-1984 attributed to the eruption of the El Chichon volcano in Mexico in 1982. Indicators such as relative humidity, water vapor pressure, wind speed, diffuse radiation, amount of fallout, average monthly temperatures, and maximum air temperature were measured in these five cities during the four seasons of the year in an attempt to find a correlation between physical atmospheric parameters and atmospheric pollution. The findings indicated that the greater the wind, the lesser the pollution, especially during the warmer seasons of the year. Figures 1; tables 1; references 4: Russian.

Molecular Study of Vaccinia Virus Genome. Part 1. Cloning of Vaccinia Virus DNA Fragments in Bacterial Vectors

917C0103A Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 24 No 4, Jul-Aug 90 (manuscript received 14 Jun 89) pp 962-967

[Article by O. I. Ryazanina, A. V. Totmenin, S. N. Shchelkunov and E. G. Malygin, All-Union Scientific Research Institute of Molecular Biology, USSR Ministry of Medical Industry, Koltsovo, Novosibirsk Oblast]

UDC 578.821

[Abstract] The importance of vaccinia virus for construction of live recombinant vaccines led to preparation and cloning of HindIII fragments of the DNA of vaccinia strain L-IVP, widely used in the USSR for vaccination. The HindIII fragments were inserted into plasmid vector pBR322, resulting in a series of plasmids designated pVH bearing all of the fragments with the exception of HindIII fragments B, G and A. The large HindIII A-fragment was cloned into cosmid pHC79 and amplified in *E. coli* DH1 to give a bank of DNA molecules bearing the large A fragment. Hybrid plasmids carrying fragments of vaccinia virus DNA may serve as vectors for introduction of foreign DNA into the vaccinia virus genome, as well as gene donors for engineering bacterial hosts for production of viral proteins. Figures 3; references 14: 7 Russian, 7 Western.

Molecular Study of Vaccinia Virus Genome. Part 2. Localization and Nucleotide Sequence of Genes Encoding Proteins 36K and 12K

917C0103B Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 24 No 4, Jul-Aug 90 (manuscript received 14 Nov 89) pp 968-976

[Article by O. I. Ryazankina, S. N. Shchelkunov, A. I. Muravlev, N. A. Netesova, N. N. Mikryukov, V. V. Gutorov, A. Ye. Nikulin, V. A. Kulichkov and E. G. Malygin, All-Union Scientific Research Institute of Molecular Biology, USSR Ministry of Medical Industry, Koltsovo, Novosibirsk Oblast]

UDC 578.821

[Abstract] Mapping studies were conducted on the late 36K and 12K genes of vaccinia virus L-IVP, with determination of their nucleotide sequence and comparison of the respective 36 kD and 12 kD proteins with a protein sequence data bank (PIR). The late genes are an area of special interest since they are located in a conservative region of the vaccinia genome and are evidently crucial to viral development. Hybridization selection of late mRNA and HindIII DNA fragments rvealed that the 36K and 12K genes were located in HindIII P-fragment. DNA-DNA hybridization studies demonstrated that the origin of the 36K gene falls within the J-fragment obtained with HindIII cleavage. Protein comparison demonstrated considerable homology between the 36 kD protein and NADH-ubiquinone-oxidoreductase and (2'-5')oligo(A)-synthase, and between 12kD protein and helix destabilizing protein and dihydrofolate reductase. Figures 6; references 25: 2 Russian, 23 Western.

Molecular Study of Vaccinia Virus Genome. Part 2. Identification of Late Gene 36K Product Located in HindIII-P Fragment of Vaccinia Virus Strain L-IVP

917C0103C Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 24 No 4, Jul-Aug 90 (manuscript received 14 Nov 89) pp 968-976

[Article by O. I. Ryazankina, S. N. Shchelkunov, A. I. Muravlev, N. V. Cheshenko, N. A. Chikayev and Z. G. Malygin, All-Union Scientific Research Institute of Molecular Biology, USSR Ministry of Medical Industry, Koltsovo, Novosibirsk Oblast]

UDC 578.821

[Abstract] An immunochemical analysis was conducted on the 36 kD protein encoded by the late 36K gene of vaccinia virus following its cloning in plasmid vector pUR290 and expression in *E. coli*. The product consisted of a chimeric protein of β-galactosidase with the 36 kD sequence representing the C-terminus. The fusion protein displayed viral specificity in immunochemical studies. Additional studies demonstrated that the 36 kD protein is not a component of the vaccinia virion per se, but of the plasma membrane of vaccinia virus-infected cells. The 36 kD protein is synthesized late in the replicative cycle in large quantities and may be important in viral assembly. Figures 6; references 12: 2 Russian, 10 Western.

Expression Unit in Initiation Region of Streptococcal Plasmid pSM19035

917C0103D Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 24 No 4, Jul-Aug 90 (manuscript received 4 Dec 89) pp 993-1000

[Article by A. V. Sorokin and V. E. Khazak, All-Union Scientific Research Center of Genetics and Selection of Industrial Microorganisms, Moscow]

UDC 579.252.58:577.214.625:577.13.5

[Abstract] An analysis was conducted on the "expression unit," EU_{19035}, of plasmid pSM19035 isolated from *Streptococcus pyogenes* and used for transformation of *Bacillus subtilis*. The nucleotide sequences of the plasmid bearing the promotor and the initiation site have been shown to be similar to those of Bacillus. Accordingly, a minimal pSM19035 replicon was engineered for expression in *B. subtilis*, incorporating a *Bacillus amyloliquefaciens* α-amylase gene lacking a promoter, a λcI857 gene with BamHI site upstream of the

ATG initiator codon. The engineered *B. subtilis* produced 0.5 g/L of α-amylase and the λ-repressor protein in an amount equal to 3 percent of the total intracellular soluble protein. The repressor was fully functional in *B. subtilis* vis-a-vis phage λP_R promoter. Additional plasmids bearing EU_{19035} were constructed (pARK11 and pCB22) with well-defined restrictase maps for use in a wide spectrum of Gram-positive bacteria. Figures 6; references 12: 1 Russian, 11 Western.

Genus-Specific DNA Probe for Yersinia Detection

917C0103E Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 24 No 4, Jul-Aug 90 (manuscript received 20 Sep 89; in final form 18 Dec 89) pp 1010-1016

[Article by G. G. Dikhanov and O. N. Podladchikova, Scientific Research Antiplague Institute, USSR Ministry of Health, Rostov-na-Donu]

UDC 579.842.23+575.222.7+577.217.34

[Abstract] Technical details are presented on the construction of a genus-specific DNA probe for the identification of Yersinia. The basic approach utilized reverse transcriptase for the synthesis of a double-stranded DNA complementary to the 5'-end of *Y. pestis* 16S rRNA. Fragments of the putative DNA probe were cloned in plasmid vector pUC19 and amplified in *E. coli.* Recombinant clones and plasmids were then cross-hybridized with P-32 labeled 16S rRNA of *E. coli* and *Y. pestis.* Plasmid DNA binding specifically to the *Y. pestis* 16S rRNA was isolated and shown to possess DNA complementary to the V1 variable region of *Y. pestis* 16S rRNA. Further hybridization studies demonstrated that the V1 region is identical in *Y. pestis, Y. pseudotuberculosis, Y. enterocolitica, Y. kristensenii* and *Y. intermedia,* and that such DNA probes are truly genus-specific. Figures 4; references 18: 2 Russian, 16 Western.

Transformation of Cotton Plants (Gossypium hirsutum L.) by Supervirulent Agrobacterium tumefaciens A281

917C0103F Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 24 No 4, Jul-Aug 90 (manuscript received 12 Dec 89) pp 1017-1023

[Article by Ye. V. Revenkova, A. S. Krayev and K. G. Skryabin, Institute of Molecular Biology imeni V. A. Engelgardt, USSR Academy of Sciences, Moscow]

UDC 579.254.2

[Abstract] Studies were conducted on the transformation of cotton plants (*Gossypium hirsutum* L.), employing cocultivation of cotyledons derived from 12-day-old shoots with *Agrobacterium tumefaciens* A281. Supervirulence of *A. tumefaciens* A281 is attributed to the presence of the supervirulence plasmid pTiBo542, which ensures a frequency of transformation some 10-fold higher than obtainable with the more commonly employed *A. tumefaciens* LBA4404. The *A. tumefaciens* A281 bore, in addition, plasmids pBII101 and pBI121 bearing the NPTII (kanamycin kinase) gene responsible for imparting kanamycin resistance. The resultant galls grew on media containing 25 mg/L kanamycin, with optimum growth and frequency of transformation enhanced on agarose MS medium. The gall tissue exhibited kanamycin kinase activity. In addition, Southern blot hybridization was used to demonstrate the presence of NPTII gene in the plant genome, further confirming the transgenic nature of the cotton plants. Figures 2; references 20: 2 Russian, 18 Western.

Economical DNA Sequencing With Terminators

917C0103G Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 24 No 4, Jul-Aug 90 (manuscript received 3 Jan 90) pp 1095-1099

[Article by A. S. Krayev and V. N. Mironov, Institute of Molecular Biology imeni V. A. Engelgardt, USSR Academy of Sciences, Moscow]

UDC 577.113.5

[Abstract] Conventional Sanger sequencing was further improved by growth of the engineered M13 bacteriophage in disposable polypropylene test tubes and by carrying out the polymerase reaction in microtritration wells. In addition, the level of label was reduced 5- to 10-fold by quasi-end labeling of the newly synthesized DNA chains with low-energy P-33 radionuclide. This technique involved synthesis of labeled chains until dNTP was depleted, followed by second synthesis for elongation of the chains until the terminator was incorporated. The use of P-33 yielded very sharp electrophoretic patterns equal to or exceeding the resolution obtained with S-35 labels, while requiring only overnight exposure with conventional x-ray film. These modifications reduce the cost of Sanger sequencing, minimize radiation hazard and offer a greater choice in the selection of label and DNA polymerase. Suitable reagents are available from 'Biopol' Scientific Production Center in Moscow and the 'Vektor' Scientific Production Association in Novosibirsk. Figures 1; references 8: 2 Russian, 6 Western.

Screening Inosine Complexes for Inhibitors of Hepatic Carcinogenesis

917C0320A Riga IZVESTIYA LATVIYSKOY AKADEMII NAUK in Russian No 10, Oct 90 (manuscript received 9 Jul 90) pp 110-115

[Article by Z. V. Rugaya, E. A. Baumanis, R. A. Paegle, M. Yu. Lidak and A. N. Kozhukhov, Institute of Organic Synthesis, Latvian SSR Academy of Sciences]

UDC 615.277.3:547.963.32'.857.3'581.04

[Abstract] Screening studies were conducted on a novel inosine complex—inosine:N,N-dimethylaminopropanol-2-ε-acetylaminocaproic acid, IOS-3161—for its efficacy against hepatic carcinogenesis. Studies on male Wistar rats with an initial weight of ca. 100 g demonstrated that IOS-3161 (50 mg/kg; i.p., alternate days for one month) was effective in slowing cancer progression resulting from a subsequent two month treatment with N-nitrosodiethylamine. The beneficial effects consisted of abatement of weight loss and an increase in the survival time from four to five months. In part, the efficacy of IOS-3161 was attributed to mitigation of lipid peroxidation. L-Ornithine decarboxylase activity was not appreciably affected by treatment with IOS-3161. Figures 5; references 18: 10 Russian, 8 Western.

Effect of Antioxidants on Hemoglobin Oxidation in Presence of Phospholipid Dispersions

917C0360A Moscow KHIMIKO-FARMATSEVTICHESKIY ZHURNAL in Russian Vol 24 No 2, Dec 90 (manuscript received 13 Dec 89) pp 7-9

[Article by M. A. Sablina, I. P. Ushakova, Ye. I. Zakharova, G. A. Serebrennikova, S. M. Alekseyev, K. A.-V. Shuaipov, and R. P. Yevstigneyeva, Moscow Fine Chemical Technology Institute imeni M. V. Lomonosov]

UDC 615.362.111.11.014.6:577.352.2].014.425

[Abstract] The effect of a number of antioxidants on hemoglobin oxidation in the presence of phospholipid dispersions was studied as part of an ongoing investigation of hemosomes (lipids with encapsulated hemoglobin) which are a convenient erythrocyte model and which may be used in researching lipid-protein interaction. The antioxidants involved were α-tocopherol and its analogs which differ in the side isoprenoid chain at position 2 of the chroman nucleus. The results demonstrated that the antioxidants effectively lengthen the period of hemoglobin functional activity in the presence of phospholipid dispersions using approximately 3 mass percent of antioxidant to the amount of lipid material. In addition, it was shown that the antioxidants α-tocopherol and derivative V (side chain of $(CH_2)_{18}CH_3$) increased the period of hemoglobin functional activity from one day (without the antioxidant, vesicular dispersion of egg phosphatidylcholine) to 28 and 30 days respectively, while the control solution, which was not exposed to lipids, was functional for 45 days. These findings suggest that lengthening the side chain at position 2 of the chroman nucleus evidently results in more effective inhibition of hemoglobin in the presence of phospholipid dispersions by means of lipid peroxidation products. Finally, the results demonstrate that phospholipids with unsaturated fatty acid radicals may be employed with the use of antioxidants in producing hemosomes. Figures 1; tables 1; references 9: 6 Russian, 3 Western.

Isoquinoline Derivative Synthesis and Antiaggregant and Hypotensive Activity

917C0360B Moscow KHIMIKO-FARMATSEVTICHESKIY ZHURNAL in Russian Vol 24 No 12, Dec 90 (manuscript received 5 Oct 89) pp 22-24

[Article by M. Yu. Dormidontov, B. Ya. Syropyatov, R. Z. Dautova, B. B. Aleksandrov, V. S. Shklyaev, M. I. Vakhrin, and A. G. Mikhaylovskiy, Organic Chemistry Institute, Ural Department, USSR Academy of Sciences; Perm Pharmaceutical Institute]

UDC 615.273.52.615.225.2]:547.833.1].07

[Abstract] Since the onset of vascular thrombosis in cases of hypertension frequently exacerbates cardiovascular disease, the development of a drug with both antiaggregant and hypotensive properties would be of great benefit. Accordingly, such a substance was sought for among isoquinoline derivatives. The results demonstrated that compounds with a methoxy group at positions 6 and 7 of the isoquinoline ring as well as an amino group and benzyl radical favor the expression of high antiaggregant activity. In addition, it was shown that compounds with an amino group and those similar to papaverine are hypotensive. The findings indicated that 3,3-dimethyl-6,7-dimethyoxy-1-(2-dimethylaminoethyl)-3,4-dihydroisoquinoline, trimethyl[2-(3,3-dimethyl-6,7-dimethyoxy-3,4-dihydroisoquinolinium-1)]-ethylammonium diiodide, and 1-(R^3-methyl)-3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinolines have the best combination of antiaggregant and hypotensive activity. Tables 3; references 8: 7 Russian, 1 Western.

Synthesis and Antiviral Activity of Substituted Piperidines and Perhydroquinolines

917C0360C Moscow KHIMIKO-FARMATSEVTICHESKIY ZHURNAL in Russian Vol 24 No 12, Dec 90 (manuscript received 19 Jan 90) pp 27-29

[Article by P. V. Reshetov, A. P. Krivenko, Ye. I. Boreko, G. V. Vladyko, and L. V. Korobchenko, Saratov University imeni N. G. Chernyshevskiy; Belorussian Epidemiology and Microbiology Scientific Research Institute, Minsk]

UDC 615.281:578.8]:[547.822.3+547.831].012.1

[Abstract] As part of the continuing search for novel highly effective antiviral preparations, a number of phenyl- and alkyl-substituted piperidines and perhydroquinolines were synthesized and their antiviral activity was investigated. These compounds were produced by liquid phase catalytic hydromethylamination of 1,5-diketones and pyrylium salts. The antiviral activity was tested on tissue cultures infected with smallpox vaccine, herpes simplex I, classical fowl plague, vesicular stomatitis, Venezuelan equine encephalitis, Echo, and respiratory syncytial viruses. As a result, two substances were found to be effective against smallpox vaccine viruses, one of which—2,6-diphenyl-N-methylpiperidine—was effective at a wide range of concentrations and nontoxic. These findings suggest that the search for potential antiviral agents among azaheterocycles with similar structures should be continued. Tables 3; references 6: 1 Russian, 5 Western.

Synthesis of Novel Antiarrhythmia Agent: Bonnecor

917C0360D Moscow
KHIMIKO-FARMATSEVTICHESKIY ZHURNAL
in Russian Vol 24 No 12, Dec 90 (manuscript received 27 Apr 90) pp 51-53

[Article by A. P. Skoldinov, A. N. Gritsenko, Kh. Vunderlikh, A. Shtark, Ye. Karstens, and D. Loman, Pharmacology Scientific Research Institute, USSR Academy of Medical Sciences, Moscow; NP [as published] Artsnaymittelwerk, Dresden]

UDC 615.22:547.869.2].012.1

[Abstract] Bonnecor (3-carbethoxyamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine chlorhydrate) is synthesized from 3-amino-5-acetyldibenzazepine, which is heated with a propanol solution of potassium hydroxide. This product is then converted into 3-carbethoxyaminodibenzazepine by means of ethyl ether of chloracetic acid. Further reaction with chloracetyl chloride yields 3-carbethoxyamino-5-chloracetyldibenzazepine, which when reacted with dimethylamine and then purified produces bonnecor. Bonnecor has been shown to be stable in light and is not oxidized in air. Results of tests in 10 clinics in the USSR and GDR have demonstrated that it is highly effective in treating various forms of arrhythmia. Bonnecor also has been shown to decrease fibrillation and has been approved for cardiological use in both countries. It is manufactured in tablet and ampul form. References 7: 3 Russian, 4 Western.

Testing for Emoxypine With Membrane Electrode

917C0360E Moscow
KHIMIKO-FARMATSEVTICHESKIY ZHURNAL
in Russian Vol 24 No 12, Dec 90 (manuscript received 14 Mar 89) pp 77-78

[Article by N. M. Kocherginskiy, N. V. Shvedene, and A. A. Shvedova, Chemical Physics Institute, USSR Academy of Sciences, Moscow]

UDC 615.272.014.425.017:615.273.52].07:543.257.1

[Abstract] A technique based on the use of a membrane electrode was proposed as a means of direct potentiometric determination of emoxypine concentration. The potentiometric measurements are performed with a digital ionometer. The membrane electrode is a cylindrical teflon shell filled with a standard emoxypine solution. Results of testing demonstrated that this membrane electrode is suitable for measuring the emoxypine concentration in aqueous solutions. Figures 2; references 5: Russian.

Effects of Dalargin on Hepatic Lipid Peroxidation

917C0308A Moscow BYULLETEN EKSPERIMENTALNOY BIOLOGII I MEDITSINY in Russian No 12, Dec 90 (manuscript received 30 Nov 89) pp 609-610

[Article by B. M. Shloznikov, R. N. Korotkina, N. V. Babkina, A. A. Karelin and Ye. P. Fomchenkov, Institute of Surgery imeni A. V. Vishnevskiy, USSR Academy of Medical Sciences, Moscow]

UDC 615.31:547.95:547.943.015.4:616.36-008.939.15-39].076.9

[Abstract] Experimental therapeutic trials were conducted with dalargin in a rat model of cholestasis and pancreatitis. The results showed that intraperitoneal administations of dalargin (10 moles/100 g) 24 h after surgery resulted in marked reduction in hepatic xanthine oxidase activity within 1 (37.6 percent), 3 (34.8 percent) and 5 (32.5 percent) h of administration. Concomitantly, hepatic dialdehyde levels fell sharply (down 43.8 percent at 3 h), while hepatic histidase activity increased by 104.3 percent in 3 h. The data were consistent with a hepatoprotective effect of dalargin via inhibition of lipid peroxidation, and suggest its use in anesthesiology in lieu of narcotic analgesics. Figures 2; references 9: 5 Russian, 4 Western.

L-Pyroglutamyl-D-Alanine (PGA) Reversal of Alcoholic Encephalopathy in In-Utero Exposed Neonatal Rats

917C0308B Moscow BYULLETEN EKSPERIMENTALNOY BIOLOGII I MEDITSINY in Russian No 12, Dec 90 (manuscript received 10 Oct 89) pp 613-616

[Article by R. U. Ostrovskaya, S. S. Trofimov, T. A. Gudasheva, N. M. Smolnikova, Ye. P. Nemova, S. V. Krapivin, N. M. Savchenko, M. L. Tsirenina, A. N. Ushakov, Ye. I. Melnik and A. B. Kampov-Polevoy, Psychopharmacology Laboratory, Institute of Pharmacology, USSR Academy of Medical Sciences; Scientific Center for Molecular Diagnostics, RSFSR Ministry of Health, Moscow]

UDC 616.831.-008.1-053.2-02:616.89-008.441.13-055.52]-085.214.3:547.745]-092.9

[Abstract] Therapeutic trials were conducted with PGA, a stable analog of piracetam, on outbred neonatal rats with alcoholic encephalopathy as a result of in utero exposure. The female rats had received intragastric administration of 5 g/kg/day ethanol in the course of gestation. The neonatal animals presented with emotional hyperreactivity, deterioration of avoidance response, EEG abnormalities, diminished cerebral levels of serotonin and elevated dopamine, and other biochemical alterations. Subcutaneous administration of 1 mg/kg PGA over days 8-19 had very beneficial effects in terms of the parameters under investigation. Consequently, these findings indicate the need for further assessment of PGA and its congeners as central stimulants with the potential of reversing or mitigating alcohol-induced encephalopathy in the developing brain. Figures 1; tables 1; references 15: 9 Russian, 6 Western.

Pharmacologic Model of Dopaminergic and Serotoninergic Mechanisms in Latent Inhibition

917C0308C Moscow BYULLETEN EKSPERIMENTALNOY BIOLOGII I MEDITSINY in Russian No 12, Dec 90 (manuscript received 12 Feb 89) pp 616-617

[Article by L. V. Loskutova and F. Ya. Lukyanenko, Department of Central Regulatory Mechanisms, Institute of Physiology, Siberian Department, USSR Academy of Sciences, Novosibirsk]

UDC 612.821.2.014.46:615.21].08

[Abstract] The neurochemical mechanisms of latent inhibition were studied on male Wistar rats, 180-200 g, subjected to 20 presentations of conditioned stimulus prior to its combination with the unconditioned stimulus. The results were compared with those derived from animals pretreated with neurotropic agents. Pretreatment (1 h) of the rats with haloperidol (0.5 mg/kg), sertraline (5 mg/kg), or combination sertraline (1 h) + bupropion (30 mg/kg; 0.5 h) gave results analogous to those with extensive presentation of the conditioned stimulus, i.e., induction of a significant delay in establishment of a conditioned avoidance reflex. Taking into cosideration the fact that the agents in question either inhibited dopaminergic mechanisms and accentuated serotoninergic mehanisms implicates these neurotransmitters in the phenomenon of latent inhibition. Figures 1; references 11: 1 Russian, 10 Western.

Antioxidant Modulation of Membranotoxic Action of Cholinesterase Inhibitors

917C0308D Moscow BYULLETEN EKSPERIMENTALNOY BIOLOGII I MEDITSINY in Russian No 12, Dec 90 (manuscript received 20 Mar 90) pp 623-624

[Article by E. P. Zatsepin, N. N. Churayev, T. A. Uspenskaya, G. D. Tirzig and G. Ya. Ddubur, Institute of Toxicology, USSR Ministry of Health, Leningrad; Institute of Organic Synthesis, Latvian SSR Academy of Sciences, Riga]

UDC 615.217.32.015.2:615.272.014.425].015.4.07

[Abstract] A series of 1,4-dihydropyrine derivatives differing in antioxidant properties were assessed for their efficacy against malathion and O,O-dimethyl-2,2-dichlorovinyl phosphate (DDP) in outbred male rats and mice. The results demonstrated that the more efficient antioxidants were also more effective in reducing

mortality following intramuscular administration of 1 LD_{50} dose of malathion, an agent strongly dependent on lipid peroxidation for its toxicity. Diludin (2,6,-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine), the most efficient antioxidant, also gave the best survival statistics when used in the pretreatment and treatment modes. DPP toxicity, which does not depend on lipid peroxidation, was not counteracted by the antioxidants. Tables 3; references 8: 6 Russian, 2 Western.

Results and Prospects for Development of Neuropharmacology in the Pharmacology Department imeni USSR Academy of Medical Sciences Academician S. V. Anichkov of the Scientific Research Institute of Experimental Medicine of the USSR Academy of Medical Sciences

917C0330B Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK SSSR in Russian No 11, Nov 90 (manuscript received 20 Feb 90) pp 16-23

[Article by Yu. S. Borodkin, I. S. Zavodskaya, N. A. Losev, Ye. V. Moreva and N. S. Sapronov, Scientific Research Institute of Experimental Medicine of the USSR Academy of Medical Sciences, Leningrad]

UDC 615.21:061.62](470.23-25)"1948-1989"

[Text] The pharmacology department of the Leningrad Experimental Medicine Institute was created in 1923. The well known pharmacologist N. P. Kravkov took charge of it; he died in 1924, however, and was unable to initiate its work. On I. P. Pavlov's advice, V. V. Savich was appointed its director, a post he continued to hold until 1934. In 1936 the department was moved to Moscow, to the newly established All-Union Institute of Experimental Medicine.

The pharmacology department was reopened in 1948 in Leningrad's Institute of Experimental Medicine, and it was headed continuously for 33 years by Hero of Socialist Labor, USSR Academy of Medical Sciences Academician S. V. Anichkov, recipient of the Lenin and State prizes. USSR Academy of Medical Sciences Academician V. M. Karasik worked together with him in the department for a long time.

The department, which now bears the name of S. V. Anichkov, is currently led by his student, Professor Yu. S. Borodkin.

For more than 40 years the department's main efforts were directed at developing research on neuropharmacology. One of the most important objectives of the latter is to study the influence of chemical agents upon neurohumoral mechanisms regulating various body functions. In this connection the successes of neuropharmacology are closely associated with wide utilization of the accomplishments of synthetic chemistry. At the same time the study and application of pharmacological substances which, as we know, serve as extremely delicate analyzers of physiological functions, made it possible to study the features of both the processes of synaptic transmission and the structure of some synaptic receptors.

Joint work by the pharmacology department and the drug synthesis laboratory (headed until 1986 by N. V. Khromov-Borisov, and presently by L. B. Piotrovskiy) promoted development of fundamental research on neuropharmacology. A fundamentally new methodology of seeking new neurotropic drugs, based on consistent change of the chemical structure of metabolites, mediators and biologically active substances closely associated with them, was developed under S. V. Anichkov's guidance [2]. S. V. Anichkov's proposal to divide cholinoreactive systems into muscarine- and nicotine-sensitive systems (M- and N-cholinoreceptor systems) was a powerful stimulus for purposeful synthesis of compounds possessing selective action in relation to these systems. The main attention was devoted to finding neuroblocking agents—central cholinolytics and adrenolytics, ganglionic blocking agents, muscle relaxants and substances imitating the structure of some natural metabolites and hormones.

It was found in the synthesis of compounds close in structure to natural biologically active substances that substances can be created that are not only similar in action to natural analogues but also possess opposite action due to competitive antagonism with natural substances.

Thus, imitating the structure of acetylcholine, specialists obtained its agonists and antagonists. A large number of choline blocking agents were synthesized and the mechanism of their action was studied on the basis of Anichkov's idea that cholinolytic substances may be created out of cholinomimetic substances by "weighting down" their molecules with aromatic acid and especially aromatic oxy-acid residues.

It is known that modern neurotropic compounds can be used to selectively affect different levels of the nervous system, from nerve endings to highly complex central nervous structures in the brain. The search for agents blocking cholinergic transmission was begun with the creation of new nondepolarizing myorelaxants (1948-1968). This was supplemented beginning in 1968 with efforts to synthesize effective ganglionic blocking agents.

Nondepolarizing myorelaxants were created on the basis of the principle of similarity with the α-tubocucarine molecule, which contains two cation groups 12.5 Angstroms apart. It was in this way that the myorelaxant paramion, subsequently approved for clinical use, was obtained. Study of the structural and conformational features of a number of newly synthesized substances made it possible for N. V. Khromov-Borisov to propose, jointly with M. L. Mikhelson in 1966 [29], a model of the tetrameric cholinoreceptor of skeletal muscles, in which the anionic centers of four cholinoreceptor monomers are located at the corners of a square around 14 Angstroms on a side. The tetrameric cholinoreceptor model

made it possible to generalize a large quantity of experimental material; however, subsequent research introduced some changes into the model [24].

Research on the conformational flexibility of bis-cationic myorelaxants and comparison of the obtained data with the type of action (depolarizing and antidepolarizing) resulted in the hypothesis that the type of action of a myorelaxant depends on the flexibility of its molecule [28]. Bis-cationic myorelaxants of rigid structure are nondepolarizers as a rule, while flexible ones are depolarizers, inasmuch as the former prevent conformational changes in the cholinoreceptor, while the latter do not. One myorelaxant with nondepolarizing action and a rigid terphenyl structure—"terkuroniy"—was approved for clinical use in 1977. Terkuroniy is close in its properties to an ideal nondepolarizing myorelaxant.

Khromov-Borisov also devoted a great deal of attention to studying the nature of intermolecular contacts of cholinergic compounds, and introduced the concept of stimulatory and inhibitory contacts.

Synthesis of highly effective ganglionic blocking agents became the next direction in the search for new neurotropic drugs. The idea that the two anionic points on a cholinoreceptor at which two cationic groups of a ganglionic blocking agent affix themselves are not identical served as its theoretical basis. Consequently it may be anticipated that ganglionic blocking agents with different cationic groups would be the most effective. Utilizing this approach, V. Ye. Gmiro obtained compounds with activity exceeding that of known ganglionic blocking agents by many orders of magnitude.

Efforts to create highly effective substances selectively blocking parasympathetic or sympathetic ganglia have special theoretical and practical value.

As Gmiro notes [9], data indicating that the ganglionic blocking effect is brought about by blocking of open ionic channels activated by acetylcholine opens up new paths of research on the dependence between the structure, activity and action of ganglionic blocking agents upon an open channel.

In addition to drugs blocking peripheral cholinoreactive biological systems, substances with a predominantly central type of action, isolated as a special group of central cholinolytics, were discovered [1,10]. Among them, methylamizil (metamizil) possessed the most pronounced M-cholinolytic properties, while methyldifacil had the most expressive N-cholinolytic properties. Torf et al. [26] synthesized a number of alkyl derivatives of amizil and difacil with radicals (methyl, ethyl, propyl) in the α- and β-positions relative to the nitrogen in their molecules. It was established that α-derivatives of amizil possess stronger central M-cholinolytic action, while β-analogues of difacil possess stronger central N-cholinolytic action. The high M-choline blocking activity is associated with presence of hydroxyl in the acid part of the molecule, which is typical not only of amizil but also of acetylene amines with structure close to it, of the phenylglycol ether of tropine, and of a number of other derivatives of benzylic acid. It is supposed that this hydroxyl group "anchors" onto the M-cholinoreceptors by means of a hydrogen bond. If we accept this supposition, then we would have to allow that the esterophilic center of an M-cholinoreceptor possesses a corresponding region capable of creating a hydrogen bond. Analysis of the pharmacological properties of a number of arecholine derivatives synthesized by N. I. Kudryashova [17] with hydroxyl groups in different positions on the piperidine ring of its molecule showed that molecules of M-cholinomimetics and M-choline blocking agents close in structure to acetylcholine apparently interact with the same active groups of a cholinoreceptor. The difference in the direction of the effects resulting from interaction of an M-cholinomimetic and an M-cholinolytic with an M-cholinoreceptor is obviously the product of conformational features of these molecules, which also bring about different conformational changes in cholinoreceptors. We studied interaction between M- and N-cholinergic mechanisms in the body for the first time under different experimental conditions [19]. Using models of arecholine and nicotine hyperkinesis, we established that the N-choline blocking agents eterofen and ganglerone block nicotine convulsions, but potentiate tremor and salivation resulting from the use of the M-cholinomimetics arecholine and aceclidine. On the other hand the M-choline blocking agents amizil and metamizil suppress the effects of arecholine and aceclidine but potentiate the duration and intensity of nicotine convulsions. It was discovered in analyzing the nature of interaction between M- and N-cholinomimetics that preliminary administration of the N-cholinomimetic lobeline suppresses manifestation of the M-cholinomimetic effects of arecholine and aceclidine, and that on the other hand the N-cholinomimetic effect of nicotine is reduced on the background of arecholine.

Differences in the directions of the effects of M- and N-cholinomimetics in the same brain structure were also discovered in research on the excitability of neuron populations of different brain structures on the background of M- and N-cholinergic drugs administered systemically and intrastructurally. In this case the action of M-cholinomimetics is suppressed by M-choline blocking agents but is potentiated by N-choline blocking agents, while the effects of N-cholinomimetics are blocked by N-choline blocking agents but are intensified under the influence of M-choline blocking agents. The results of our own experiments and published data allowed us to formulate the conception of reciprocity of the interaction between M- and N-cholinergic mechanisms within the bounds of the same cholinergic system of the body [19]. Knowing that choline blocking and choline potentiating drugs are widely used by clinical specialists to correct various pathological states, though without regard for interaction between M- and N-cholinergic mechanisms, we decided to study the possibility of capitalizing on this phenomenon as a way to raise the effectiveness of treating such diseases. With this

purpose we used a number of experimental models of various pathological states in animals. We established that blocking of N-cholinoreactive biological systems with ganglerone or eterofen and stimulation of M-cholinoreactive biological systems with galantamine have anticonvulsive action in epileptogenic models brought about by injection of penicillin into the dorsal division of the hippocampus of rabbits and "stimulation" of the amygdaloid nucleus in cats. The anticonvulsive action is significantly intensified with simultaneous blocking of N-cholinoreactive and stimulation of M-cholinoreactive biosystems.

It was established by experimental modeling of Parkinson's syndrome (akinesia, muscle rigidity, tremor) in animals by the use of large doses of galantamine (simulation of parasympathetic hypertension in the central nervous system) that blocking of M-cholinoreactive biosystems suppresses manifestations of Parkinson's syndrome, while on the other hand N-choline blocking agents potentiate their intensity and duration. In this connection we propose combining the blocking of M-cholinoreactive biosystems with simultaneous stimulation of N-cholinoreactive systems in the treatment of Parkinson's patients. Clinical tests of this approach revealed it to be more effective than the traditional treatment method using M-choline blocking agents alone or their combination with L-DOPA drugs. In addition the effectiveness of adreno- and dopaminomimetics increases significantly on the background of the combined use of matamizil and galantamine, inasmuch as the doses of L-DOPA drugs are decreased by a factor of 3-5.

A model of compensation of limb motor function in response to extirpation of the contralateral zone of the motor cortex in cats, which simulates affliction of the brain's pyramidal system, was used to demonstrate a significant decrease in the time of recovery of limb function in response to intraperitoneal injection of ganglerone or galantamine, as compared to recovery time in control animals. The effectiveness of these drugs is increased even more with their combined use. On the other hand administration of metamizil significantly lengthens the time of compensation of limb motor function in cats in comparison with the same in the control group [27]. The results of these experiments provided the grounds for proposing ganglerone in combination with galantamine as a means of treating spastic forms of children's cerebral paralysis dominated by symptoms of an impaired pyramidal system.

It was discovered in a study of the safety of using M-choline blocking agents together with acetylcholinesterase (ACE) inhibitors that at larger doses it significantly expands the therapeutic breadth of action of the latter as far as transition to a neuromuscular block, in connection with which the decurarizing property of proserine increases significantly; signs of overstimulation of the parasympathetic system are absent in this case.

Moreover it was established that balanced reciprocal interaction between M- and N-cholinergic mechanisms plays an important role in regulating functions in the central nervous system and its peripheral division. These observations were used in the treatment of patients with afflictions of peripheral nerve trunks. Research directed at raising the effectiveness of treating ulcers, hypertension and bronchial asthma is currently proceeding.

The results of our research and published data also indicate that an interdependence exists at all levels of the body between the action of acetylcholine and catecholamines, between acetylcholine and 5-OT [not further identified], between acetylcholine and GAMK [not further identified], and so on; change in the concentration of a number of mediators and substances connected with them in different organs and tissues of the body are the product in this case of primary change of the acetylcholine level. In this connection N. A. Losev formulated the idea that the cholinergic mechanism is a basic one (relative to other mediator systems), combining and regulating the function of somatic, autonomic, hormonal, immune, memory and other systems of the integral organism. Normal function of this mechanism is supported by an optimum relationship in the level of reciprocal interaction between M- and N-cholinoreactive biosystems within the bounds of the same cholinergic system of the body.

On the basis of this conception we feel it suitable to propose a new approach to pharmacological correction of a number of persistent pathological states brought about by affliction of the peripheral and central divisions of the nervous system—that of blocking M-cholinoreactive biosystems and simultaneously stimulating N-cholinoreactive systems, or on the other hand, blocking N-cholinoreactive systems while simultaneously stimulating M-cholinoreactive biosystems. Clinical tests on this approach revealed it to be highly effective.

In addition to creating various cholinergic substances, the pharmacology department synthesized a number of central adrenolytics [16]. Thus compounds possessing central adrenolytic activity (fepratset and the drug IEM-611) were obtained by joining p-aminophenylacetic and p-dialkylaminophenylacetic acid residues to the nitrogen on the indirect sympathomimetic phenamine. Microinjections beneath a stimulating chemical electrode made it possible to establish that fepratset possesses β-adrenoblocking action, and that its activity is comparable with that of propranolol, while IEM-611 possesses α-adrenoblocking action superior to that of phentolamine.

It was shown later on in a special series of studies that drugs possessing pronounced antiarrhythmic properties (bis-(β-phenylisopropyl), polymethylenediamines) can be created by changing the structure of phenamine and norepinephrine, which influence cardiac contraction rhythm [15].

Efforts were made in the department in recent years to create substances selectively acting upon histamine-sensitive receptors. Comparison of the effects of histamine itself and triazole derivatives closely related to it made it possible to arrive at an impression of the structure of the H_1- and the H_2-receptor. The most significant difference lies in the presence of a lipophilic zone in the H_1-receptor and a hydrophilic zone in the H_2-receptor. Introduction of a hydrophilic radical into the triazole molecule makes the compound capable of eliciting intense secretion of gastric juices, which is inherent to excitation of H_2-receptors. Compounds possessing a lipophilic radical elicit spasms in smooth muscles as a result of excitation of H_1-receptors. The original drug tidazin, which selectively excites H_2-receptors, was created on the basis of these laws. Tidazin passed clinical tests successfully and was recommended for use in a diagnostic test to reveal impairments in gastric juice secretion.

Anichkov's idea of creating new drugs by imitating the structure of natural metabolites led to the synthesis of an entire class of compounds—derivatives of imidazole- and pyrazoledicarboxylic acids. The neurotropic drugs etimizol and its derivatives, obtained by this means, are the most interesting. It was found that etimizol is capable of significantly increasing the concentration of cyclic AMP in tissues, as a result of which oxidative phosphorylation and anaerobic glycolysis are intensified. This leads to accumulation of energy resources in tissues in the form of energy-rich phosphates, and creatine phosphate in particular. Analysis of the molecular mechanism of action of etimizol established that it affects the adenylate cyclase system, activating adenyl cyclase and inhibiting the activity of phosphodiesterase. Etimizol's ability to directly activate adenyl cyclase distinguishes it from the methylxanthines (theophylline, caffeine), the effect of which is restricted to an inhibitory effect upon the enzyme phosphodiesterase.

It may be supposed that the action of the drug upon energy metabolism is at the basis of its diverse pharmacological effects. As we know, etimizol stimulates respiration, increases secretion of ACTH-glucocorticoids and possibly influences memory processes. Etimizol is now being used in medical practice to accelerate repair processes, as a stimulator of tissue energy metabolism.

One of the traditional directions that developed successfully under the guidance of S. V. Anichkov is research on the neuropharmacology of endocrine functions. A reflex relationship was demonstrated for the first time between carotid chemoreceptors that are highly sensitive to pharmacological agents and biochemical changes, and endocrine glands. This relationship was registered in 1973 as a discovery. Neuroendocrinological research was also conducted on the participation of various central nervous system mediators in regulation of the activity of the hypophyseo-adrenocortical system. An analysis conducted using pharmacological substances influencing particular biochemical mediator systems of the brain (cholinergic, adrenergic, serotoninergic and others) revealed that regulation of the functional activity of the hypophyseo-adrenal system involves a system of several mediators. Use of selectively acting adrenoblocking and cholinoblocking drugs under the conditions of changing intracentral relationships and redistribution of the "load" upon control centers, brought about by exclusion of certain discrete zones of the hypothalamus, provided a possibility for obtaining new information on the unequal distribution of cholinoreactive and adrenoreactive systems in the hypothalamus participating in regulation of secretion of ACTH-glucocorticoids. It was shown that cholinoreactive systems are localized in the mammillary region, α-adrenoreactive systems are localized in the posterior and anterior divisions, and β-adrenoreactive systems (playing an inhibitory role) are localized in the ventromedial region of the hypothalamus [23].

The results of electrophysiological, pharmacological and biochemical research made it possible to derive the general principle of regulation of the hypophyseo-adrenal system, according to which numerous systems are generally responsible for central regulation of secretion of ACTH-glucocorticoids in the body—a system of different mediators and different functional formations of the brain. In this case each of them has independent significance, as is evidenced by experiments involving administration of mediators and stimulation and inhibition of different sections of the brain, while at the same time they are also interrelated elements of one overall regulatory system.

Another direction of the work of the pharmacology department is study of the effect of neurotropic drugs upon intracentral interaction between different brain systems and structures.

The mechanism of action of centrally active substances was studied, and the locations of their action upon specific brain formations were determined [6]. Systemic administration of neuromediator substances (agonists of neuromediators and their antagonists), their direct injection into brain structures by means of chemical electrodes and brain incisions at different levels were laid at the basis. Cholinergic agents (metamizil, arecholine, nicotine), adrenergic compounds (norepinephrine, amphetamine, α- and β-adrenoblocking agents), neurohormones (ACTH, vasopressin), etimizol, ethanol, and many other pharmacological agents were analyzed. This research resulted not only in determination of the locus of action of substances upon specific brain structures but also a detailed EEG characterization of the regional distribution of neuromediator receptors in different systems and formations of the central nervous system. Moreover in a number of cases this research made it possible to satisfactorily explain the nature of dissociation of EEG manifestations and behavioral changes elicited by some pharmacological substances (metamizil, etimizol). The nature of the influence of synaptotropic agents on excitability of the cerebral cortex became decisive to determination of the mechanism of their

action upon animal behavior. The principle of intracentral regulation of brain structures was also found to be irreplaceable and extremely productive in research on basic phenomena of brain activity such as memory and learning. It was revealed that these brain functions can be optimized, irrespective of the nature of their neuromediator support, by raising the excitability of the ascending activating reticular formation of the brain stem and the cerebral cortex while optimally inhibiting limbic formations and structures associated with the extrapyramidal system and the diencephalon. Such an effect was produced by optimum doses of cholinopositive and adrenopositive substances, serotonin-negative drugs, and etimizol. The reverse interrelationships were observed in the action of serotonin-positive agents, antiadrenergic and anticholinergic drugs, and ethanol, which impaired memory and learning. These compounds raised the excitability of structures of the limbic complex, significantly reducing the functional activity of the midbrain's reticular formation and (or) the cerebral cortex [5,6]. Determination of the nature of influence of synaptotropic agents and antifeine derivatives on long-term memory and reproduction of memory traces is a natural continuation of this research [7]. It was persuasively demonstrated that a number of antifeine derivatives are characterized by extremely pronounced positive influence upon the indicated processes [4,5]. In this case the action of one of these compounds—etimizol—on long-term memory was observed independently of the system and form of learning and the emotional sign of reinforcement, which made it possible to view it as a "nonspecific connector" which reinforces, upon its administration after learning, all changes elicited by learning in central nervous system activity. These facts were laid at the basis of developing and stabilizing artificial stable functional relationships in the human brain through direct electrostimulation of brain structures [25], which was used for therapeutic purposes against central motor disorders. Significant attention was devoted to studying the molecular mechanisms at the basis of the optimizing effects of antifeines upon memory and learning. It was found that activation of the RNA-synthesizing neuron system is the most significant link in the chain of events determining the biochemical mechanism of long-term memory activation by antifeines. Such activation is the result of direct interaction of the substances with genetic structures in brain cells. The existence of acceptor proteins in the neuron nucleus responsive to antifeines was confirmed later on by data indicating that they have an effect on the activity of cyclic AMP-independent chromatin protein kinases, which are responsible for phosphorylation of nonhistone acid proteins. Removal of this protein fraction from chromatin completely eliminates the etimizol effect associated with stimulation of RNA synthesis [18]. Such direct action upon the cerebral genome by means of specific pharmacological compounds opens up a new possibility for a truly specific search for substances capable of correcting pathologically altered memory in the clinic.

S. V. Anichkov was the first pharmacologist to propose and develop I. P. Pavlov's idea on nervous regulation of trophic processes and on its disturbance as the cause of neurogenic dystrophy. Anichkov's teaching on the pharmacology of neurogenic dystrophy is the basis for organic unification of experimental pharmacology with physiology, pathology and biochemistry; it opened up broad possibilities for using experimental data in clinical medicine. The pharmacology department has been conducting an intensive search for neurotropic compounds influencing neurogenic afflictions of internal organs for many years. Models most adequate to diseases in relation to which the nervous factor has dominant significance (neurogenic afflictions of the heart, vessels, stomach, liver, pancreas and lungs) were developed for experimental pharmacotherapy [3].

Detailed pharmacological analysis of the development of neurogenic afflictions of internal organs made it possible to reveal their reflexive nature, and the great significance of the sympathetic nervous system and its mediator, norepinephrine, in their development. The phenomenon of adrenergic mediator depletion as the cause of development of neurogenic dystrophy was registered in 1971 as a discovery. The data of biochemical pharmacology made it possible to establish that neurogenic afflictions of internal organs arising in response to extreme influences upon the body (stress) are the result of disturbed energy and plastic metabolism. Information indicating reduction of the concentration of macroergic compounds—creatine phosphate and ATP, reduction of the level of cyclic AMP and of the intercellular concentration of calcium ions, reduction of the membrane potential of mitochondria, and reduction of the overall level of nicotinamide nucleotides and their oxidized forms attest to discoordination of tissue metabolic processes, including energy forming processes [12,13]. When many pathological phenomena develop, peroxide lipid oxidation (PLO) is known to become impaired, as a result of which changes occur in the permeability of biological membranes. It was established that the level of malonic dialdehyde and fluorescing Schiff bases in myocardial tissue and blood serum increased by 50 percent in animals subjected to extreme effects. Similar changes were noted in joint clinical-experimental research in blood serum from patients with myocardial infarctions and cardiac ischemia. It was concluded on the basis of the obtained data that the level and dynamics of changes in PLO processes can serve as an additional diagnostic and prognostic sign of cardiovascular pathology. Similar disturbances of PLO were observed with neurogenic and ischemic damage to the stomach and other organs of the digestive tract. A close mutual relationship was noted between impairment of PLO processes, shifts in the balance of endogenous catecholamines and energy supply to tissues of the damaged organ [21,22].

It was shown that when neurogenic visceral pathology develops, the activity of the cellular genetic apparatus undergoes restructuring. The insufficiency of genetic processes manifests itself as a decline in the DNA/

protein ratio in the nuclear fraction of gastric, myocardial and brain cells, as reduction of the ratio of histones to DNA, and as a decrease in the rate of uptake of ^{14}C-uridine into isolated nuclei of cells of damaged organs, which is an indication of suppressed RNA synthesis. Impairment of genetic activity, which promotes induction or repression of so-called key enzyme systems, has a negative effect on the body's adaptive functions in extreme conditions [20].

Study of the central mechanisms responsible for development of visceral pathology elicited by extreme effects upon the body revealed a relationship between destructive damage to internal organs and metabolic changes in the central nervous system [8]. Disturbance of the metabolism of the most important brain neuromediators is evidence that different neuromediator processes are involved in the central mechanism of transmission of damaging pulses to target organs (Table 1). An imbalance arises in this case between acetylcholinergic, catecholaminergic and GAMK-ergic mediator systems, which also play an important role in the genesis of dystrophic phenomena. It should be kept in mind that GAMK is viewed today not only as an inhibitory transmitter but also as a substance capable of influencing synthesis of other mediators (dopamine, norepinephrine). It is also well known that synaptic transmission mediators contribute to regulation of energy metabolism, controlling the rate of synthesis and concentration of enzymatic and isoenzymatic proteins. This is why changes in the neuromediator balance inevitably affect the course of biological energy processes in brain tissues.

Table 1. Effect of Three-Hour Electrostimulation and Immobilization in the Subthalamic Region of the Rat Brain on Indicators of Neuromediator Metabolism

Indicator	Number of Experiments	Control	Stimulation	% of Control
Norepinephrine, μg/gm tissue	10	0.96 +/- 0.08	0.22 +/- 0.03****	23
Dopamine, μg/gm tissue	10	1.80 +/- 0.16	0.47 +/- 0.05****	26
DOPA, μg/gm tissue	10	0.18 +/- 0.04	0.08 +/- 0.02**	44
Homovanillic acid, μg/gm tissue	8	0.16 +/- 0.02	0.09 +/- 0.02**	56
Serotonin, μg/gm tissue	11	0.76 +/- 0.04	0.50 +/- 0.02****	66
Monoamine oxidase, μg serotonin/gm tissue/hr	9	20.5 +/- 1.67	9.9 +/- 0.71****	48
Acetylcholine, μg/gm tissue:				
free	11	0.8 +/- 0.10	0.44 +/0 0.15*	55
bound	11	1.6 +/- 0.13	0.52 +/- 0.20****	32
Cholinesterase, mg acetylcholine/gm tissue/min	8	4.6 +/- 0.29	6.8 +/- 0.32****	149
GAMK, μg/gm tissue	15	368 +/- 30	260 +/- 20***	71

Note. *—$p<0.05$, **—$p<0.025$, ***—$p<0.005$, ****—$p<0.001$

Table 2. Effect of Three-Hour Electrostimulation and Immobilization of Rats on Indicators of Brain Energy Metabolism

Indicator	Number of Experiments	Control	Stimulation
Succinate dehydrogenase, units/mg tissue/hr	6	72 +/- 6.2	39 +/- 3.0
Cytochrome oxidase, units/mg tissue/hr	6	26 +/- 2.0	13 +/- 1.5
Creatine phosphate, μmoles/gm tissue	6	2.6 +/- 0.17	1.0 +/- 0.08
High molecular weight isoenzyme creatine kinase, μmoles/mg tissue/min	10	0.55 +/- 0.03	0.33 +/- 0.01

Inasmuch as the central nervous system's energy metabolism is the determining factor of its activity, impairment of brain tissue energy supply can be one of the leading causes of development of persistent pathological states, and of visceral pathologies in particular.

Our experiments showed that extreme effects upon an animal's nervous tissue also elicit changes in energy metabolism (Table 2).

Thus the disturbances we discovered in metabolism of a number of neuromediators and in the brain's energy metabolism attest to disturbance of trophic processes in brain tissue, which doubtlessly affects the trophic state of organs.

It was concluded from the research that disturbance of closely interrelated processes—functions of the cell's genetic apparatus, bioenergetic processes and protein synthesis—lies at the basis of the development of neurogenic damage to internal organs elicited by extreme effects upon the body.

Experimental studies and theoretical generalizations have been confirmed fully through joint research with

clinical specialists—cardiologists and gastroenterologists. It was established that profound ultrastructural disturbances are observed in the myocardium and that the tissue level of norepinephrine and the concentration of creatine phosphate in biological preparations of heart tissue decrease by the end of surgery in patients operated on for congenital and acquired heart defects. Prescription of the norepinephrine precursor L-DOPA prevents ultrastructural and biochemical changes and it has a favorable influence on the course of the postoperative period, as well as of the repair period in patients with myocardial infarctions and tonsilogenic cardiopathy.

Data obtained in clinical conditions indicate that energy insufficiency exists in the time of aggravation of gastroduodenal diseases. A sharp decline in the concentration of creatine phosphate is noted in biopreparations from the periulcerous zone of the gastric and duodenal mucosa in the presence of ulcers, and in patients with chronic gastritis coupled with secretory insufficiency.

Summarizing the data obtained in pharmacological analysis of the mechanism of development of neurogenic damage to internal organs, we can conclude that central neuroblocking agents, ganglionic blocking agents and peripheral adrenolytics effectively prevent development of experimental damage to internal organs when administered beforehand. However, these same substances inhibit tissue metabolism and retard healing of ulcers when administered at the same doses after application of a stimulus in the repair period [11].

It was experimentally substantiated that use of neurotropic drugs that restore the activity of the sympathetic nervous system and its mediator, norepinephrine, and which normalize energy and plastic metabolism in tissues would be suitable in the pharmacotherapy of neurogenic damage to internal organs. One such drug is L-DOPA, which promoted recovery of mediator reserves, the level of cyclic AMP and the activity of creatine kinase, normalized tissue metabolism, increased the energy resources in tissues and hastened repair processes. Etimizol had the same kind of therapeutic action.

Clinical and experimental research on use of neurotropic drugs to treat gastroduodenal and cardiovascular systems made it possible to propose a fundamentally new system for treating ulcers, myocardial ischemia and myocardial infarctions depending on specific conditions and the stage of treatment of the disease. It was substantiated that prescription of neuroblocking agents to patients would be suitable only in the acute period of illness, when an excessive flow of nervous impulses that evoke and maintain the pathological process is noted. However, when acute phenomena cease and the repair phase sets in, suppression of nerve impulses may slow down repair processes. In this stage, as follows from experimental and clinical data, drugs that normalize the trophic function of the sympathetic nervous system and stimulate tissue energy metabolism are indicated. Such drugs are L-DOPA, etimizol and some of its derivatives [4].

Detailed analysis of data from biochemical and clinical pharmacology and the results of clinical observations open up broad prospects for studying the pathogenic mechanisms of neurogenic damage to internal organs, and determine the basic directions for the search for drugs to be used in pharmacological correction of neurodystrophic diseases of the gastrointestinal tract and the cardiovascular system. Neurotropic substances that promote recovery of the activity of the sympathoadrenal system and its mediators, normalization of energy resources and tissues, and synthesis of the key enzymes of metabolic processes may turn out to be extremely useful not only for prevention but also for pharmacotherapy of diseases of internal organs having etiology and pathogenesis dominated by the nervous factor.

As concerns the pharmacology department's future research, there are good prospects in seeking new drugs influencing bioenergetic processes in tissues and the neuromediator balance, and in creating highly effective nootropic drugs that correct brain function disorders, adaptogens, antihypoxants, antioxidants, calcium antagonists, and analogues of stimulatory and inhibitory amino acids. A significant amount of attention will be devoted to analyzing interactions of the brain's opiate systems with biogenic amines, and on this basis, to seeking pharmacological resources that reduce tolerance of and dependence on this ethanol.

Research in genetic pharmacology will be an important subdivision of the department's work. There are plans for seeking pharmacological substances influencing phosphorylation of basic histone proteins in the cell genome and promoting induction and repression of key enzyme systems performing an adaptive function in the face of extreme effects upon the body. The results of this research will make it possible to significantly widen the arsenal of resources used to treat cerebral ischemia, epilepsy, Parkinson's disease, and thinking and memory disorders in the presence of aging and alcholism.

The data of experimental and clinical pharmacology will provide a possibility for taking new approaches to treating diseases such as myocardial ischemia, myocardial infarction, hypertension and ulcers.

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Effects of Neonatal Irradiation on General Behavior and Maze Performance in Rats

917C0312A Tbilisi IZVESTIYA AKADEMII NAUK GRUZINSKOY SSR: SERIYA BIOLOGICHESKAYA in Russian Vol 16 No 5, Sep-Oct 90 (manuscript received 6 Apr 89) pp 293-297

[Article by I. M. Ayvazashvili and D. E. Gelitashvili-Papidze, Institute of Physiology imeni I. S. Beritashvili, Georgian SSR Academy of Sciences, Tbilisi]

UDC 612.821

[Abstract] X-irradiation (7 Gy/min, 5 min) of the heads of 5-day-old outbred suckling rats resulted in behavioral abnormalities that persisted for 35 days. The essential features consisted of general attenuation of locomotor activity and deterioration in maze trials. In addition, the irradiated rats displayed delayed physical development, with the weight of the experimental animals reaching 85 g after three months versus 110 g for control animals. The full spectrum of CNS damage remains to be analyzed, but altered myelination pattern appears to be one of the factors responsible for the behavioral sequelae. Figures 2; references 9: 7 Russian, 2 Western.

Adsorption of Fusicoccin to Bilayer Lipid Membranes (BLM) and Transport of Hydrophobic Ions

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[Article by G. V. Tivadze, M. D. Kandelaki and G. I. Daneliya, Regional Branch, All-Union Scientific Resarch Institute of Agricultural Biotechnology, Tbilisi]

UDC 577.352

[Abstract] In order to better understand the mechanism of action of the plant growth regulator fusicoccin (FC), a product of Fusicoccum amig, an assessment was conducted of its effects on BLMs. Studies with BLMs prepared from azolectin (I) and dioleylphosphatidylcholine (II) showed that addition of FC resulted in different changes in the BLMs, depending on their chemical nature. Adsorption of FC to I BLM resulted in reduction of ionic permeability to structural compaction of the membrane, whereas the opposite effect in the case of II BLM led to an increase in permeability. Studies with protonophore pentachlorophenol demonstrated that introduction of FC into the BLM system resulted in appearance of a transmembrane potential which corresponded to $[H^+]$ on the side free of FC. Evidently, one of the mechanisms of action of FC on plant cells involves stimulation of the proton pump and regulation of intracellular pH. Figures 4; references 21: 3 Russian, 18 Western.

Pressing Problems of Modern Radiobiology in the Light of Assessing and Forecasting the Consequences of the Accident at the Chernobyl Nuclear Power Plant

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[Article by A. V. Sevankayev and A. N. Dedenkov, Scientific Research Institute of Medical Radiology, USSR Academy of Medical Sciences, Obninsk, under the rubric "Investigation of Consequences of the Accident at the Chernobyl Nuclear Power Plant," first paragraph is RADIOBIOLOGIYA introduction]

UDC 577.391.621.311.25.004.65

[Text]The authors validate important directions of basic research at this stage of development of radiobiology in the light of assessment and prediction of the sequelae of the Chernobyl accident: problems of low doses, radiation carcinogenesis, radiation embryology, distinctions of internal radiation, combined effect of radiation and environmental chemicals, etc.

The intensive development of atomic power and nuclear technologies, the ever-increasing use of ionizing radiation in industry, medicine, research; the potential danger of local nuclear accidents which, as shown by the events at the Chernobyl Nuclear Power Plant (CNPP), acquire catastrophic dimensions, all this requires considerable intensification and expansion of basic research in radiobiology. At the present stage of its development, particularly with reference to assessment and prediction of adverse consequences of the CNPP accident, radiobiologists are faced with a number of problems and concrete tasks that demand immediate resolution.

Of course, this pertains first of all to investigation of the biological effects of low radiation doses. The question of low doses is one of the most important and, at the same time, most difficult problems of radiobiology and radiation medicine that have not yet been definitively resolved. The current assessments of the risk of adverse consequences of low levels of radiation are, as we know, based on extrapolation of effects of high doses to low ones. The validity of such an approach is being actively discussed at present among specialists, and arguments are being advanced both for and against the feasibility of such extrapolation. One of the main reasons for being forced to use extrapolations to assess the effects of low doses is that there are no clear-cut quantitative data in radiobiology and radiation genetics about their biological effects. It is difficult to obtain such data because, in order to carry out such investigations, it is necessary to use very radiosensitive test systems characterized by a distinct quantitative dependence of biological effect on dosage in the case of the lowest possible levels of exposure. It is believed that a human lymphocyte culture is among the few such test systems. Indeed, the low

spontaneous level (average of 1.0-1.5 percent) of chromosome aberrations in peripheral blood lymphocytes of healthy subjects and, conversely, high radiosensitivity of human chromosomes, as compared to those of other species, permits reliable recording of induced structural damage in them at rather low doses, on the order of a few cGy. The fact that the frequency and types of chromosome aberrations are the same with identical exposure of lymphocytes *in vitro* and *in vivo*, i.e., external and internal radiation, is an equally important property of this test system [1]. The latter property of lymphocytes offers a rare opportunity to carry out experimental cytogenetic radiation investigations directly with human cells, thereby avoiding one more interspecific extrapolation, when studies are carried out on other models, which inevitably adds to the inaccuracy of finite (large dose) extrapolation estimates of the effects of low radiation doses, i.e., avoiding double extrapolation of biological effects.

The difficulty of obtaining objective information about cytogenetic effects of low radiation doses lies in the relatively low level of aberrations in this dose range. Therefore, in order to obtain an accurate enough quantitative evaluation of their mutagenic effect it is necessary to analyze too large a number of metaphases with such doses, something like a few thousand per dose. The difficulty and laboriousness of cytogenetic analysis naturally delays development of research in this direction. Nevertheless, to date several such studies have already been published, including our own, which dealt with the quantitative patterns of yield of chromosome aberrations in human lymphocyte cultures exposed to low (less than 50 cGy) radiation doses [2-8]. The main conclusion drawn from the results of these studies is that quantitative patterns of formation of structural chromosome damage in the genome of human somatic cells exposed to low doses differ somewhat from the effects of higher doses.

As we know, the conception of linearity and absence of threshold is the basis for extrapolation estimates of genetic effects of radiation carried out at the present time. However, analysis of the above-mentioned studies does not allow us to make an unequivocal judgment as to the nature of cytogenetic effects as a function of dosage in the range of low radiation doses, since the results of these investigations turned out to be rather contradictory: in some cases the yield of aberrations corresponded more to a linear function [2, 4, 6], in others to a quadratic-linear one [5], and in others yet a more complex dependence was reported [3, 7, 8]. Yet a more thorough analysis of these studies revealed that, in absolutely all of the cases, there was indeed a more complicated yield of aberrations than simply linear or quadratic-linear function, and it was characterized by the presence of a plateau on the dose curve, the only difference being that it was manifested for different dose ranges in the reports of different authors. Such an anomalous dose-effect function in the range of low doses persisted even when radiation dose rate was changed by a factor of 10^2 [8]. In some of the cited works, extrapolation of the cytogenetic effect of high doses to low ones resulted in finding an effect that was higher than expected [3]. It should be noted that there are also indications in the literature of analogous anomalous dose-effect function in the range of low radiation levels with respect to radiation carcinogenesis, in particular oncogenic transformation of cells, and in this case too low doses or dose rates induced a greater effect than expected with extrapolation from high doses [9, 10]. In the opinion of some authors [11], one cannot rule out the possibility of approximately 10-fold underestimation of biological effectiveness of low radiation doses. On the other hand, there are data in radiobiology about the stimulating and adaptive effects of low radiation doses. There was even appearance of a corresponding term, "radiation hormesis," which implies a beneficial effect of low doses of ionizing radiation.

Thus, to conclude this brief discussion of problems of low radiation doses, it must be stated that, with today's level of knowledge in radiobiology and radiation genetics, we do not yet have reliable quantitative data about biological effects of low radiation doses, and therefore are not in a position to determine unequivocally whether extrapolations from high doses are exaggerated or, on the contrary, understated estimates of the risk of low levels of radiation. Assessment of risk will depend appreciably on which mathematical model is used to describe the dose-effect function in the range of low radiation doses. This is valid at least, as shown above, for structural mutations in human somatic cells.

It should be stressed that the uncertainty of the dose-biological effect function in the range of low levels of radiation makes it difficult to solve a number of problems that have basic (radiation mutagenesis and carcinogenesis) and applied importance (evaluation and prediction of genetic and carcinogenic risk, sanitary and hygienic standard-setting, biological dosimetry, and others). This question acquires particular acuity in our times in connection with the CNPP accident. For this reason, it is necessary at present to increase considerably and expand basic radiobiological investigations in this direction, and to do this on all levels of biological organization: molecular, genetic, tissular-cellular and organism as a whole.

The problem of radiation carcinogenesis has always been important at all stages of development of radiobiology, but it acquires particular urgency because of the CNPP accident. According to WHO data, 90 percent of the malignant neoplasms occurring in man are attributable to the effects of environmental factors. According to current conceptions, genome instability plays the deciding role in initiation of carcinogenesis. The above-mentioned similarity of cytogenetic effects and oncogenic cell transformation due to exposure to low radiation doses can, to some extent, speak in favor of this hypothesis. It is therefore deemed important to develop research on genome stability and determination of the mechanisms of its destabilization. At the present time,

numerous variants of DNA damage that destabilizes the genome as a whole, and the role of repair enzymes in eliminating this damage and maintaining genome stability have been well-studied. There has been considerably less study of the nature of so-called irreparable genome damage compatible with cell life but which renders it more sensitive to subsequent exposure to deleterious factors, such as radiation and chemical mutagens, viral invasion, activation of oncogens, and others. There are experimental facts indicative of persistence of genome instability in the offspring of irradiated cells. In general, however, the problem of genome stability and mechanisms of its destabilization is still far from being solved, and it merits the closest scrutiny of radiobiologists.

The enormity of radioactive contamination of territories as a result of the CNPP accident raises acutely the question of assessing and forecasting the health status of offspring of people who live there. The answer to this question requires in-depth investigation of the effects of radiation on germ cells and the fetus at different stages of their development. Yet we have limited information as yet concerning the radiosensitivity of reproductive (particularly female) cells and fetus of mammals in the course of their morphological and functional development when exposed to low radiation doses and environmental chemical agents in the environment. Prenatal development, which is characterized by intensive cell proliferation, differentiation and migration of cells, is a process that is highly radiosensitive. Exposure to radiation during pregnancy can lead to fetal destruction, developmental disturbances, deformities, functional deviations and formation of tumors in childhood. The first trimester is considered the period of extremely high risk of deformities, severe mental deficiency and induction of tumors [12-14]. And, as shown by the results of investigations in Hiroshima and Nagasaki, exposure to radiation in the period from the 8th to 15th weeks of pregnancy, even in doses of 0.01-0.02 Gy, doubles the number of cases of severe mental retardation, whereas starting at a dosage of about 0.5 Gy one observes a rise, which is proportionate to dosage, in number of cases of this serious pathology. The specifics of the effects of incorporated radionuclides on gonads and fetus, with consideration of the nature of their distribution and formation of absorbed doses in the body, occupy a special place in this problem. The actual ecological situation that exists today following the CNPP accident, requires comprehensive investigation of the effects of the above environmental factors on parental gonads, course of pregnancy, and fetal development at all stages of ontogenesis, including its postnatal period. Yet, we must note with regret that in recent years there has been some decline in the study of experimental radiation embryology in our country. However, the social importance of development of basic research in this direction is obvious, considering the extent of contamination of territories and number of people living there.

An equally important problem at the present time, which is related to radioactive contamination of vast territories as a result of the CNPP accident, is to investigate the distinctions of internal irradiation, in particular due to incorporated radionuclides of iodine and cesium. As we know, there are several specific features of internal irradiation that distinguish it from external exposure. We refer, first of all, to spatial and time-related nonuniformity of distribution of absorbed dose due to the distinctions of distribution of radioactive atoms in biological structures and their transport in the body. The second typical feature of internal irradiation is the appreciable contribution to the biological effect of so-called transmutation phenomena that accompany the act of atom decay (energy of nuclear radiation, excitation of atoms, emission of a cascade of low-energy electrons of the Auger type, etc.). Comparative experimental studies have shown [16] that, when Auger-emitting atoms get into functionally important microstructures, the absorbed doses in the latter may be many times greater (tens or hundreds of times greater in some cases) than mean absorbed doses in larger biostructures containing them (for example, in cells or nuclei of cells as a whole, respectively). Hence the biological effect will also be determined by the radiation burdens in functionally important microstructures (for example, chromosomes), rather than by the mean accreted doses in larger biostructures that contain the former. It is remarkable that when Auger emitters are incorporated in relatively less vitally important cell structures (membranes, cytoplasm) their biological effectiveness diminishes dramatically. For this reason, true understanding of the observed biological effects of internal irradiation and, consequently, feasibility of forecasting them scientifically, is possible only with consideration of macro- and microdistribution of absorbed doses of a given radionuclide. Unfortunately, the approaches that are traditional in radiobiology often make the mistake of using averaged characteristics: mean absorbed doses for an organ or the body as a whole, without consideration of the time of their formation.

Speaking of the distinctions of internal irradiation, we cannot fail to also mention the fact that dosimetry of internal irradiation also has its own distinctions, as compared to dosimetry for external exposure, and it also requires further development and refinement. In this respect, it is extremely important to always use the same, unified system of measuring absorbed doses which, on the one hand, would tie in with analogous systems used in other countries and, on the other hand, would permit corrections and additions, for example, with consideration of age, presence of pathology, as well as the need to assess distribution of absorbed doses on the level of biological microstructures.

In contaminated areas, not only are the inhabitants exposed to a higher radiation background, but also the constant presence (to some degree or other) of chemically active compounds in the environment, which reach the soil and water as a result of often unwise industrial activities of man. One should not overlook the typical property of some chemical compounds of interacting

directly (forming chemical bonds) with genetic structures of the cell, in particular, DNA molecules, which renders them genetically even more "aggressive" than other mutagenic factors. Information has appeared to the effect that even relatively indifferent chemical compounds, such as nitrates, which are used the most in our agricultural practice and are not per se active chemical mutagens, can cause 4- to 6-fold enhancement of the mutagenic effect of radiation. For this reason, it is important to develop research on mechanisms of interaction between lesions induced by radiation and toxic environmental chemicals, and determination of possible adverse synergism of their combined effect in order to evaluate and predict risk factors to the public residing in contaminated areas with different levels of radiation and chemical backgrounds.

An important place is reserved for the search for effective radioprotective agents against relatively low doses of radiation, in the case of long-term internal and external exposure, in order to prevent and minimize the adverse long-term sequelae of the CNPP accident. The problem of pharmacochemical protection of germ cells, pregnant women and the fetus due to their extremely high radiosensitivity, merits particularly serious attention.

As indicated by the results of examining victims of the accident, immunity plays an important part in the body's reaction to radiation. In this regard, it is also deemed important to expand investigations of immunological status in the case of long-term exposure to low doses of external and internal radiation combined with other deleterious factors.

We should also include among the pressing tasks for modern radiobiology development of rather simple and accessible methods of biological tracers and radiation dosimetry, particularly in the range of low doses. Along with the traditional but rather complicated method of biological dosimetry based on metaphase analysis of chromosome aberrations, more recently specialists are placing some hope on the micronuclear method of evaluating cytogenetic damage in binucleate cells [17] and, first of all, in the range of low radiation doses [18-20], the glycophorin test, and others.

Of course, there are more problems in modern radiobiology than the directions of research mentioned above. Nevertheless, in our opinion, if expressly these problems are solved first, it will be possible to offer a scientifically validated assessment and forecast of the sequelae of the CNPP accident.

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Effect of Pentacine on Subcellular Distribution of ^{239}Pu-Nitrate in Rat Lungs

917C0445A Moscow MEDITSINSKAYA RADIOLOGIYA in Russian Vol 36 No 2, Feb 91 (manuscript received 17 Jan 90) pp 49-51

[Article by N. R. Kabirova and A. L. Sokhranich, Biophysics Institute, USSR Ministry of Health, Moscow]

UDC 616.24-008.927.994.02.239-033.1-092.9-07

[Abstract] As part of the search for novel methods of eliminating plutonium from the body, the subcellular location of ^{239}Pu-nitrate in the respiratory organs and the effect of pentacine on ^{239}Pu-nitrate uptake was investigated on 200 female Wistar rats (0.18 + 0.02 kg). The experimental group inhaled a 5 percent solution of pentacine 30 min prior to the administration of 106 Bq of ^{239}Pu-nitrate to all of the animals. Results of differential centrifugation and gel filtration demonstrated that the radionuclide accumulates selectively and is strongly bound by the nuclear fraction, probably due to the formation of stable complexes between ^{239}Pu and the DNA. Three hours after inhaling the ^{239}Pu-nitrate, 34.4 percent of the radionuclide is bound with subcellular organelles, 6.8 percent of which is bound to the nuclear fraction. This figure rises to 12.2 percent by 24 h. It was also shown that inhaling pentacine prior to ^{239}Pu administration decreases the radionuclide concentration in the subcellular fractions and organelles of the lungs by 22 percent. However, pentacine was not effective in eliminating ^{239}Pu-nitrate from hyaloplasm proteins. Figures 1; tables 2; references 4: Russian.

Somatic Cell Genome of Animals Following Extended Radiation Exposure

917C0445B Moscow MEDITSINSKAYA RADIOLOGIYA in Russian Vol 36 No 2, Feb 91 (manuscript received 17 Jan 90) pp 51-54

[Article by G. G. Rusinova, V. A. Turdakova, and G. S. Mushkacheva, Biophysics Institute, USSR Ministry of Health, Moscow]

UDC 616-001.28-092.9-07:[616.438+616.419]-008.93:577.113]:577.213.7

[Abstract] The changes in the various levels of the structural organization of DNA in response to repeated radiation exposure were investigated in male Wistar rats (140-160 g). The animals were exposed daily to 0.5 Gy doses of ^{137}Cs gamma radiation, with total doses ranging from 0.5 to 20 Gy. Analysis performed one day subsequent to the last exposure demonstrated a 51-60 percent decrease in the number of thymocytes and bone marrow cells. With doses up to 20 Gy, this figure remained the same for the bone marrow cells, but continued to decrease to 23 percent for the thymocytes. Furthermore, substantial alterations to the DNA structure of the bone marrow and thymus were noted following prolonged daily exposure. Results of spectrofluorimetric investigation revealed persistent alterations in the primary structure of thymocytic DNA due to the depressed level of DNA (70-83 percent of the control) following a total absorbed dose of 2.5 Gy, but no such changes were noted for the bone marrow cells. In addition, conformational changes in the nucleoid of both tissues attest to rearrangement of genome activity. These results suggest that radiation exposure elicits a need for rearrangements to change the regulation of the genome and switch gene activity to a new regimen of replication, transcription, and reparation. Figures 3; tables 2; references 13: 10 Russian, 3 Western.

Gamma Spectrometer Measurement of Radionuclide Concentration in Biological Specimens

917C0445C Moscow MEDITSINSKAYA RADIOLOGIYA in Russian Vol 36 No 2, Feb 91 (manuscript received 16 Nov 89) pp 55-57

[Article by V. N. Vasilyev, MNIRRI [as published], RSFSR Ministry of Health]

UDC 615.471.03:616-001.28-008.923.6.02.134/.137-073.916

[Abstract] This paper presents the construction of a spectrometer-radiometer based on mass production models. It provides a simultaneous count in a radiometric channel and spectrometric analysis that simultaneously processes signals from several detectors. This scintillation spectrometer-radiometer has been developed for use in practical radiation monitoring as well as for research purposes. The spectrometer comes equipped with a lead shield, scintillation detector, low- and high-voltage supply lines, single channel analyzer for rapid radiometric counting in an energy window, and spectrometric analyzer for identifying the nuclides and determining the isotopic composition of the specimens. The average mass of the specimens is 100-200 g, with an average measurement time ranging from 100 to 1,000 seconds, depending on specimen activity. The minimum detectable concentration is (0.5-1.0) x 10^{-9} Ci/kg (18.5-37 Bq/kg). Figures 2; tables 1; references 2: 1 Russian, 1 Western.

Third All-Union Conference on Genetics and Cytology of Meiosis

917C0188 Novosibirsk IZVESTIYA SIBIRSKOGO OTDELENIYA AKADEMII NAUK SSSR: SERIYA BIOLOGICHESKIKH NAUK in Russian No 2, Aug 90 pp 24, 29, 33, 37

[Selected abstracts of reports from conference in Novosibirsk, Sep 90]

[Excerpts] [Passage omitted]

Maksimov N. G., Sharma P. M., Maksimova V. I., Totskiy V. N. **Meiosis in Hybrids of Octoploid Triticale with Soft Wheat.** All-Union Breeding and Genetics Institute, Odessa; Odessa State University im I. I. Mechnikov [p 24]

Wheat-rye allopolyploids (2n = 8x = 56) of the genome composition AABBDDRR are of interest for the transmission of economically important characteristics from rye to wheat. F_1 hybrids in the majority of cases had 49 chromosomes of the genome composition AABBDDR. Theoretically, in metaphase I of the meiosis, 21 bivalents (21_{II}) and 7 univalents (7_I) should be formed in such hybrids. It was experimentally established that the formation of chromosomal associations varies from $17_{II}15_I$ to $23_{II}3_I$, which attests to a substantial deviation of the synapsis process from the theoretically expected $21_{II}7_I$. Not only the chromosomes of the rye genome, which are not genetically related, but also some of the chromosomes of the wheat genome, are in the univalent state. Fewer conjugating chromosome pairs than theoretically expected is due to the presence of the rye genome, which causes disharmony in the conjugation of chromosomes of wheat genomes. An increase in the number of pairing chromosomes is caused either by autosyndesis of the R genome (rye-rye) chromosomes, or by allosyndesis (wheat-rye). In spite of the substantial disruptions in all the phases of meiosis, the hybrid plants F_1 have relatively normal productiveness as a result of the elimination of the univalent chromosomes. On the average, up to 24.5 grains per spike are formed.

Thus, the complex mechanism of conjugation and recombination makes it possible to create forms of soft wheat with the genetic information of rye, which is of interest for breeding. [passage omitted]

Bondar L. M., Chastokolenko L. V. **Abnormalities in Meiosis of Vicia Cracca L. Exposed to Various Anthropogenic Factors.** Scientific Research Institute of Biology and Biophysics of Tomsk State University [p 29]

An analysis of meiosis is carried out in plants from populations with diverse ecological stress levels: from a region with an operating high-voltage electric power transmission line, from along a highway with heavy traffic, from a region with a petrochemical plant (the city of Tomsk) and with Novokuznetsk industrial enterprises, and from a radioactively contaminated zone (chronic irradiation over a period of 20 years).

An increase in sterility, caused to a considerable extent by disruptions in meiosis, is observed in zones of anthropogenic pollution. No specific anomalies exclusively characteristic of that zone were detected. A rather standard collection of disturbances, connected with chromosomal rearrangement and the pathology of the cleavage (division) spindle, is noted. The specific characteristic of the effect consists in the variation in relationships of certain anomalies that is a function of the operating factor. For example, with chronic irradiation the formation of all kinds of bridges and fragments is most typical. In plants growing along a highway, numerous disturbances are brought about by the underdevelopment of the microtubules or other pathology of the division apparatus. Such anomalies are frequently associated with disturbances in the SH-groups, whose blockers are mercury, lead and a number of other metals. One of the most toxic components of exhaust gases is lead. Thus, one of the mechanisms of the harmful effect of motor vehicle exhaust gases on meiotic is traced. [passage omitted]

Romanova I. M., Lysikov V. N. **Abnormal Meiosis in Corn in Pollination With Pollen Irradiated With High Doses of Gamma Radiation.** Institute of Ecological Genetics, MSSR Academy of Sciences, Kishinev [p 33]

The effect of high doses of gamma radiation causes the fragmentation of DNA in irradiated pollen. When this pollen is employed in pollination, individual genes are transmitted from the paternal forms to the offspring. A combination of chromatin dispersion, mutagenesis and transformation takes place.

In corn plants obtained as a result of pollination with pollen irradiated by high doses, the meiosis of the second generation was studied. During the pachytene, frequent breaks in corn chromosomes were observed at doses of 300 and 1000 Gy with a frequency of 15.8 + 1.5% and 36.5 + 2.4%, and also terminal deletions, disconjugation of the chromosomes; in diakinesis, univalents and open bivalents were observed; in metaphase I, lagging of the chromosomes and their nonuniform passage to the poles; in anaphase I, individual fragments. The plants carried either male or female sterility. Transformants and mutants with abnormal caryopses were obtained.

Recently, a number of authors have shown that the frequent breaks in corn chromosomes were caused by a system of mobile elements, and they occur in a section where the *Ds* element is located and another element (*Ac*) is absent.

It is possible to assume that in this case the chromosome breaks are associated with the formation of *Ds* sections as a result of the transfer of individual genes of irradiated pollen. [passage omitted]

Nikitin A. I., Slozina N. M., Kitayev E. M., Vorob'yeva O. A. **Study of Meiosis in Man and Problem of Conception Hygiene.** Institute of Obstetrics and Gynecology, USSR Academy of Medical Sciences, Leningrad [p 37]

At the present time, questions associated with "improving the quality of our progeny" are acquiring more and more importance in the context of improving the health of the human population. It has been shown that the reproductive process and, in particular, one of its most important stages—the realization of meiosis—can suffer from deteriorating ecological conditions, as well as from the active intrusion of sociocultural factors into the reproductive process rhythms that have come about through evolution and from the spreading of, for example, harmful habits through neurohormonal regulational mechanisms. The development of infertility and various forms of congenital pathology (chromosomal diseases, defects, etc.) can be a consequence of its disruption. A working hypothesis for the regulation and mechanisms of disturbances of the meiotic process in mammals and man is proposed. The question has been raised about the necessity of developing a special area—"conception hygiene"—whose basic objective should be to work out recommendations on questions concerning the selection of the most optimum conditions for the planning of pregnancy and the protection of the periovulatory period, during which the completion of the meiotic process occurs.

225th Anniversary of the Moscow Medical Academy imeni I. M. Sechenov of the USSR Ministry of Health

917C0330A Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK SSSR in Russian No 11, Nov 90 p 3

[Selected articles devoted to the anniversary of the I. M. Sechemov Moscow Medical Academy.]

[Text] The Moscow Medical Academy imeni I. M. Sechenov of the USSR Ministry of Health (subsequently the Academy) was founded in 1765 as the medical faculty of Moscow University. The Academy contains two therapeutic faculties, a public health and hygiene and a pharmaceutical faculty (with an evening department), a department of medical technology (operated jointly with the Moscow Higher Technical School imeni N. E. Bauman), a preparatory department, and faculties that raise the qualifications of instructors for the advanced training of physicians and the advanced training of pharmacists. A new faculty for the training of science educators began its work on 1 September 1990. The Academy possesses its own clinics (with 2,520 beds), on the basis of which scientific schools historically evolved and are constantly developing, and a large experimental base.

The academy is the head training and methodological center of the USSR State Committee for Public Education and the USSR Ministry of Health in developing, testing and introducing new forms and methods of teaching future specialists. The conditions at the Academy make it possible to train specialists on the basis of the lastest scientific accomplishments. The departments possess possibilities for thorough study of subjects by students, and their participation in scientific work.

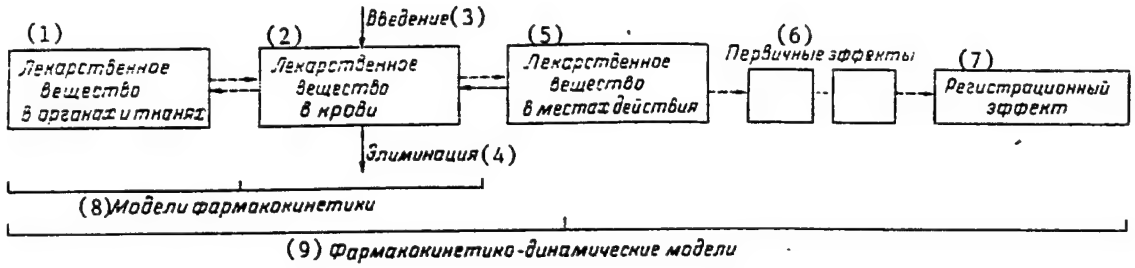
Over 8,000 students, 200 graduate students, 600 resident physicians, 10 doctoral candidates and 420 foreign citizens (including 80 graduate students, resident physicians and trainees) from 46 of the world's countries are studying concurrently in the Academy. Pedagogical, scientific and therapeutic work is carried out in 100 departments, seven of which are operating on the basis of scientific research institutes of the Ministry of Health and the USSR Academy of Medical Sciences. Twenty-six academicians and corresponding members of the USSR Academy of Sciences, 20 merited scientists of the RSFSR, over 40 recipients of the Lenin and State prizes and the Council of Ministers Prize, and six heroes of the Soviet Union and Socialist Labor are doing educational work in the Academy. Each year the Academy's scientists publish around 40 monographs and collections, 45 textbooks and training manuals, and 2,000 articles.

Eleven specialized scientific councils awarding the academic degrees of doctors and candidates of sciences are functioning in the Academy. Large numbers of personnel of higher qualifications (competitors, resident physicians, graduate students, doctoral candidates) are being trained in the departments for medical institutions of higher education of the country and foreign countries.

For over two centuries the Academy was one of Russia's major cultural centers. Its graduates always participated actively in the country's social and political life. Voices in support of many progressive and humanitarian initiatives were heard on many occasions behind the walls of the medical faculty of Moscow University. With the society's renewal in our country, development of these noble traditions acquired new quality and scope in the Academy's collective, taking on humanitarian content and a new way of thinking.

Devotion, charity, the desire to do good for the people without compensation and to bring the light of knowledge to fellow citizens, and patriotic public service always distinguished the Academy's graduates, the real physicians and intellectuals of Russia. These traditions were constantly supported. And they are alive and developing today as well. It was through the persistent appeals of the Academy's community to the USSR government that the physician's oath was restored, to become a mandatory state act in the solemn initiation of all graduates of medical schools as physicians.

Many professors, instructors, scientists, physicians and nurses of the Academy provide assistance to practical public health in Moscow, to dozens of cities and towns in the country, and to the medical services of plants, factories and institutions without compensation. Scientists and physicians generously share their knowledge with associates, and they treat patients in the most remote regions of the country, in northern and eastern regions, in the Nonchernozem and in all union republics. Scientists and students of the Academy provided emergency care to victims of earthquakes (in Peru, Algeria, Uzbekistan and Armenia) and of the accident at the



Key:
1. Drug in organs and tissues
2. Drug in blood
3. Administration
4. Elimination
5. Drug in places of action
6. Primary effects
7. Recorded effect
8. Pharmacokinetic models
9. Pharmacokinetic-dynamic models

Chernobyl Nuclear Power Plant with a deep understanding of their high duty as physicians. Professors and graduates of the Academy were the initiators and founders of higher medical educational institutions in different regions of the USSR. Hundreds of the Academy's graduates actively promoted establishment of public health and medical education in many of the world's countries, and participated in the implementation of many United Nations WHO and UNESCO programs within the framework of broad international cooperation.

Under the conditions of perestroyka, cooperation with the new public movements (the USSR Culture Fund, the Charity and Health Fund, the Children's Fund imeni V. I. Lenin) is developing within the walls of the Academy. The Academy is a group member of the USSR Culture Fund, together with which it is implementing the program "Through Culture to Health and Charity." Important movements of the medical community such as the all-union associations of medical VUZes and medical students came into being within the walls of the Academy.

The Presidium of the USSR Academy of Medical Sciences warmly congratulates the collective of the Moscow Medical Academy imeni I. M. Sechenov of the USSR Ministry of Health on its 225th anniversary, and wishes it new successes in training medical personnel and in its scientific, therapeutic and preventive work.

Possibilities of Mathematical Modeling in Pharmacokinetics

917C0330C Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK SSSR in Russian No 11, Nov 90 (manuscript received 18 Jul 89) pp 60-64

[Article by V. K. Piotrovskiy, Scientific Research Institute of Prevention of Noninfectious Diseases, VNITs PM (not further identified) USSR Ministry of Health, Moscow]

UDC 615.2/.3:033:519.86

[Text] Mathematical modeling of pharmacokinetics is one of the most swiftly progressing areas of this science, which is itself developing more intensively on the whole than any other subdivision of pharmacology. In addition to the traditional spheres of application of mathematical methods—modeling of the absorption, distribution and elimination of drugs, the branch of pharmacodynamics is also being actively subjected to quantitative description. As a result integrated pharmacokinetic-dynamic models embracing practically the entire complex of phenomena, from introduction of a drug into the body to its therapeutic effect (see diagram), have arisen and are enjoying increasingly more widespread application. This article briefly examines the basic approaches used in modeling pharmacokinetics and the problems which are being successfully solved today by means of modeling or which may be solved in the near future.

Table 1 shows the basic groups of mathematical models used to describe pharmacokinetics. Three levels of complexity of the models are distinguished in the left side of the table; these levels also reflect the degree of their approximation of reality. It increases from the bottom up; the degree of detail in the models rises as well. But the number of assumptions also increases concurrently. As a result models at the highest level have rather narrow application as a rule. The lowest level provides the most general description, and it is limited only by global conditions—for example the condition that the system be linear, that it be a steady-state system, and so on.

Table 1. Classification of Basic Pharmacokinetic Models

Level of Detail	Types of Models	
Structural Models	Physiological	
	Chamber	Veng-Pedersen's Systemic Approach
Empirical models	Stochastic	Volumatic
Model-independent description	Statistical moment method	

The basic types of models used today in pharmacokinetics are shown on the right side of the table. They are arranged in a certain order in relation to the left part of the table, which reflects the level of detail inherent to them.

The statistical moment method is at the lowest level. It employs practically no assumptions concerning the structure of the system, and it permits assessment of only the fundamental parameters of pharmacokinetics—total clearance, average retention time and its variance, and distribution volumes [1].

Immediately above the statistical moment method are two classes of models which may be treated quite rightly as empirical models. They differ significantly from each other in their initial premises. Postulation of a certain distribution function for the times of retention of drugs in the body [5] and for absorption times (when describing extravascular administration) [19] is typical of stochastic models. These models are the most widely encountered in pharmacokinetics. They include mono-, bi- and triexponential functions, which are commonly used to approximate the dependence of drug concentration in blood (plasma) after intravenous administration.

Many feel that use of such functions is equivalent to employing chamber models (a monoexponential function corresponds to a one-chamber model, a biexponential function corresponds to a two-chamber model, and so on). But this opinion is wrong in the general case. Only for a monoexponential function is this valid; in the case of a biexponential stochastic model, as many as three different chamber models providing the same biexponential function exist.

Volumatic models are based on empirical functions of the dependence of the drug distribution volume in the body on time [20]. This is a new class of models that has not yet enjoyed wide application; however, its possibilities are such that these models will surely be used in many branches of pharmacokinetics.

On the whole, the chamber models most widely used in pharmacokinetics occupy an intermediate position, since they may be empirical in some cases (it is precisely in this quality that they are used as a rule in pharmacokinetics [6]), and structural in others (when their structure is based on anatomical and physiological data [11]).

Recently Veng-Pedersen proposed an original and highly promising approach [25], which essentially entails redefining the basic concepts of pharmacokinetics—elimination and distribution. The overall structure of the model is close to that of a two-chamber model. This is why this approach is located in the overall scheme (see Table 1) between the empirical and the structural level, since it combines the traits of both the one and the other. In this model, all flows of a drug from a central chamber into peripheral organs and tissues, or to the outside in general (that is, excretion and metabolism) are combined under the name "elimination." The rate of the latter depends exclusively on the concentration of the drug in the central chamber. Besides other things, such a wording permits us to include the case of nonlinear elimination in the examination. This is a major step forward in comparison with empirical stochastic models, in which only the linear case is considered.

On the other hand the entire flow from the periphery into the central chamber is called "distribution"—the reverse of traditional ideas. A general equation is derived on the basis of the material balance; however, it can be practically solved only in relation to polyexponential functions, and thus this approach may be viewed as a detailed version of polyexponential stochastic models.

The upper level in the hierarchy of the types of pharmacokinetic models is occupied by physiological models, which can describe the entire set of pharmacokinetic processes with whatever accuracy desired, at least theoretically, but in this case the solution rests upon the need for experimental assessment of an enormous quantity of parameters, which sharply limits the applicability of this class of models—in any case for clinical and biopharmaceutical purposes [2].

Going on to an examination of the approaches used to describe the entire chain of phenomena—from administration of the drug dose to the recorded pharmacological effect (see diagram), we should emphasize that the picture is still far from complete in this regard. Nonetheless, the successes that have been attained permit the hope that it is precisely along this path that we will find the solutions to the principal problems of pharmacokinetics, which is of practical interest only when "it says something to us about pharmacodynamics" [17].

Simultaneous description of pharmacokinetics and pharmacodynamics is possible within the framework of integrated pharmacokinetic-dynamic models, which include, as is clear just from the name itself, two rather independent parts—pharmacokinetic and pharmacodynamic (Table 2).

Pharmacokinetic and Pharmacodynamic Components of Integrated Pharmacokinetic-Dynamic Models

Pharmacokinetic Models	Pharmacodynamic Models
Stochastic	Linear
	Logarithmic
Chamber	Hyperbolic
	Sigmoid (Hill's equation)
Physiological	

Generally speaking the former may be any model of the types examined above (only three types that have enjoyed practical application are shown in Table 2). The latter formulates the law by which the observed effect is associated with the concentration of the drug in the region of the organism in which the structures reacting to

the drug (receptors etc.) are located. This region may be called the effector zone. Table 2 shows the types of functions used today for quantitative expression of this relationship.

The concentration of a drug in the effector zone cannot be measured directly as a rule. Only its concentration in blood (plasma) can be practically determined. Two fundamentally different cases are possible in graphic analysis of the dependence of the observed effect on drug concentration in plasma.

First, the curve may have a monotonic trend, where an increase in concentration corresponds with growth of the effect, while a decrease corresponds to its reduction. It may be assumed in this case that the drug concentration in the effector zone is directly proportional to its concentration in blood. This is possible if exchange of the drug between the effector zone and blood occurs significantly faster than other drug mass exchange processes occurring in the body. The integrated pharmacokinetic-dynamic model, which corresponds to this case, is relatively simple. Its pharmacodynamic component is in a sense the "superstructure" above the pharmacokinetic model, and it directly associates drug concentration in blood (plasma) with observed effect.

Presence of hysteresis, or a loop, where the effect is delayed in relation to concentration, is an alternative variant of the dependence of effect on drug concentration in blood. In this case, for example, with intravenous administration the concentration decreases monotonically, while the effect first grows and then begins to decrease. It would be natural to suppose that the drug concentration in the effector zone is not proportional to its concentration in blood. This is possible if the speed with which the drug is delivered to its place of action is comparable to the rates of other drug transport processes in the organism. Mathematical description of this situation requires that we kinetically isolate the effector zone and then associate it with the rest of the organism. This idea was formulated for the first time by Segre within the framework of chamber pharmacokinetic models [21], and it was later developed in the works of Sheiner [15,23]. This is presently the most widely used approach in integrated pharmacokinetic-dynamic modeling. In particular, it allows us to account for the contribution of active metabolites to the overall effect of drugs [16]. However, chamber pharmacokinetic models are not the only variant that can be used in the creation of an integrated model. A similar result may be arrived at by using stochastic models as the pharmacokinetic component of the integrated pharmacokinetic-dynamic model [4].

Great are the possibilities of physiological models in building integrated models [10], but their current use is clearly inadequate, at least for clinical purposes.

Completing this brief survey of the most important approaches used in modeling pharmacokinetics, we can say that the currently existing possibilities allow us to solve practically any specific problem. In many cases there are several models providing practically identical results, and the choice between them is but a matter of taste or preference. In particular, stochastic models can almost always produce the same results as chamber models. Continued wide use of the latter is only out of tradition, inasmuch as these were the first mathematical models used in pharmacokinetics.

Let us examine the typical problems of pharmacokinetics that can be solved by mathematical modeling.

1. Estimation of the individual values of pharmacokinetic parameters and their biological accessibility under experimental and clinical conditions. This is one of the principal tasks of pharmacokinetic research, since only by means of pharmacokinetic parameters reflecting particular processes can we quantitatively describe the latter and assess the influence of various factors on them [3]. Empirical models and, in part, chamber models (in this application the structure of the model does not necessarily have to correspond to a real situation; all that is important is the shape of the resulting curve), are the most convenient for this purpose. Volumatic models having clearance and distribution volume (stationary or kinetic depending on the means of administration [5]) as their parameters are also extremely convenient.

2. Assessment of average population values of parameters and their distribution. Besides the standard method of such assessment, which entails statistical treatment of individual data obtained in a representative sample, there exists a method based on describing, within the framework of a particular pharmacokinetic model (chamber or stochastic), a set of data accumulated in the course of controlled treatment of a large group of patients with a particular drug (therapeutic monitoring). In this case a small number of blood samples are taken from each patient in order to determine the concentration of the drug, which is why it is almost impossible to estimate individual values of the parameters. Nonetheless by using some methods of regression analysis we can assess not only the average population values of pharmacokinetic parameters but also the characteristics of their dispersal and even the influence of various factors on pharmacokinetics [24].

3. Prediction of individual profiles of the concentration of a drug and its metabolites. By having selected a model for a specific set of concentration-time data after one-time administration, and having assessed the model's parameters, we can calculate the concentration profile for the given individual in the case of chronic administration relatively easily. When we are concerned with the concentration of a drug in blood, stochastic and chamber models are the most convenient for this purpose.

4. Assessment of the concentration of drugs in organs and tissues, and the dynamics of this concentration over time. Solution of this problem requires an adequate structural model describing the real process of mass transfer of the drug between different organs and tissues.

As a rule, what we use in this case are physiological (perfusion) models, in which we can account for all details of the drug's distribution and elimination [12], but sometimes we also use chamber models, especially when sufficiently complete data are unavailable (for example when the concentration of a drug is known only in one target organ).

5. Calculation of dosing conditions ensuring a maximum impact at minimum risk of side effects. This is the main task of clinical pharmacokinetics, one which can be carried out both within the framework of ideas about therapeutic range and with the use of integrated pharmacokinetic-dynamic models. In the first case it would be sufficient to use stochastic or chamber models to predict the concentration of the drug in blood in the case of chronic administration (see above), and the dosing conditions can be selected or calculated in such a way that the resulting level would be maintained within an interval known for the drug in question—between the minimum effective and the maximum safe level. The so-called Bayyesovskiy [transliteration] method of optimizing drug dosage is based on this approach [27]. The second approach accounts for the real trend of the concentration-effect dependence [8]. Also it is more general, since it can be used in principle for drugs having an effect that is not associated directly with their concentration in blood. So-called dynamic models *in vitro* are an original application of modeling pharmacokinetics with the purpose of optimizing dosing conditions [7].

6. Calculation of dosing conditions with regard for the temporal dynamics of pharmacokinetic characteristics. We know that when a large number of drugs are taken many times, changes occur in the body's enzymatic systems responsible for metabolism of the drugs (induction and inhibition phenomena). These phenomena may be accounted for within the framework of pharmacokinetic models—chamber and stochastic models in particular. When we use such models to optimize treatment, we can calculate dosage more accurately and avoid overdoses or prescription of ineffective doses. An even more difficult problem arises when it becomes necessary to consider cyclic variations in certain processes in which the drugs participate in the body (chronopharmacokinetics). The circadian rhythm is the most important. It can be accounted for in principle by chamber or stochastic models used for optimization of treatment. However, these approaches have not yet been developed adequately.

7. Interspecific transfer of pharmacokinetic data. There are several approaches making it possible to use data obtained on one or several species of animals to predict pharmacokinetics in another species, and in man in particular [13]. The apparatus of physiological models is the strictest and best substantiated. It provides a possibility for calculating the concentration profiles of drugs both in blood and in the organs of any species of animals on the basis of data on regional circulation and protein binding indicators [14]. In this case the structure of the model is based on anatomical and physiological data, and as a rule it is a general model for all species of mammals.

8. Determination of the profile for the rate of delivery of time-release drugs into the systemic channel. In recent years we have seen the appearance of many forms of drugs differing in their method of delivery, in which a particular predetermined profile of drug release rate is used to maintain a therapeutic level of the drug for a long time in blood after one-time use. In developing such forms, we need to monitor both the kinetics of release *in vitro*, and the rate of delivery into the systemic channel *in vivo*. The apparatus of stochastic models and convolution-deconvolution procedures are the optimum mathematical resources for solving this problem [26].

9. Prediction of the kinetics of drug metabolism in an individual organ and in the body as a whole, according to data on enzymatic activity *in vitro*. Such prediction has become possible as a result of over 15 years of active research on the modeling of hepatic elimination of drugs. The latest work on this subject [9,18] shows that thorough examination of the processes involved makes it possible to describe complex situations and solve both the direct problem (prediction of the rates of processes on the basis of known model parameters) and the inverse problem (assessment of model parameters).

Concluding our examination of the possibilities of mathematical modeling in pharmacokinetics, we should dwell on the urgent problems of pharmacokinetic science which would be impossible to solve without the use of pharmacokinetic models.

Thus, to solve the problem of synthesizing substances with a prescribed spectrum of properties, which is required for purposeful creation of new, most effective and safe drugs, we would have to bring together, into a single unit, research currently developing in parallel on quantitative relationships between drug structure and activity and between structure and pharmacokinetics [22]. The binding link in such a unification could be integrated pharmacokinetic-dynamic models, which will apparently make it possible to predict chemical structures optimum both from the standpoint of pharmacological activity and in relation to pharmacokinetics.

It may be supposed that in the near future we will be able to create a general approach that will make it possible to design and manufacture forms of drugs which could be delivered to the systemic channel on the basis of a prescribed program, with the latter accounting for all features of pharmacokinetics and pharmacodynamics, including changes in them—in particular, induction or inhibition of enzymes, change in the body's sensitivity to the drug (for example, of tolerance to it) and so on.

Finally, without the active use of pharmacokinetic modeling methods, it would be impossible to create forms of drugs that can be delivered directly to their place of action. No matter what the mechanism of such delivery

might be (liposomes, immune vectors etc.), its realization will require quantitative consideration of distribution, binding, elimination and other processes that the new drugs will experience.

Summarizing the above, we should emphasize that without broad introduction of the methods of mathematical modeling of pharmacokinetics, it will be impossible to achieve further progress not only in this discipline but also in pharmacology as a whole.

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